"CURRENT PATTERN OF ENTERIC FEVER IN CHILDREN: A PROSPECTIVE CLINICAL AND MICROBIOLOGICAL STUDY"

Dissertation submitted for

M.D DEGREE EXAMINATION

BRANCH VII – PAEDIATRIC MEDICNE

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INSTITUTE OF CHILD HEALTH AND

HOSPITAL FOR CHILDREN

MADRAS MEDICAL COLLEGE

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CERTIFICATE

This is to certify that the dissertation titled **"Current Pattern Of Enteric Fever In Children: A Prospective Clinical And Microbiological Study"** submitted by **Dr. MOHAMED REBOIS, A.M.,** to the Faculty of Pediatrics, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D. Degree (Pediatrics) during the academic year 2012 – 2015 is a bonafide research work carried out by him under our direct supervision and guidance.

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DECLARATION

I solemnly declare that this dissertation entitled **"Current Pattern Of Enteric Fever In Children: A Prospective Clinical And Microbiological Study"** was done by me at Madras Medical College and Institute of child health, during 2012-2015 under the guidance and supervision of **Prof. Dr.T.Ravichandran, M.D, D.C.H.** This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree in Pediatrics (Branch-VII).

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Date : Signature of Candidate

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INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To

Dr.Mohamed Rebois.A.F,
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Dear **Dr.Mohamed Rebois.A.F,**

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "**Current Pattern of Enteric Fever in Children: A prospective Clinical and Microbiological Study**" No.16042014.

The following members of Ethics Committee were present in the meeting held on 08.04.2014 conducted at Madras Medical College, Chennai-3.

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We approve the proposal to be conducted in its presented form.

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The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

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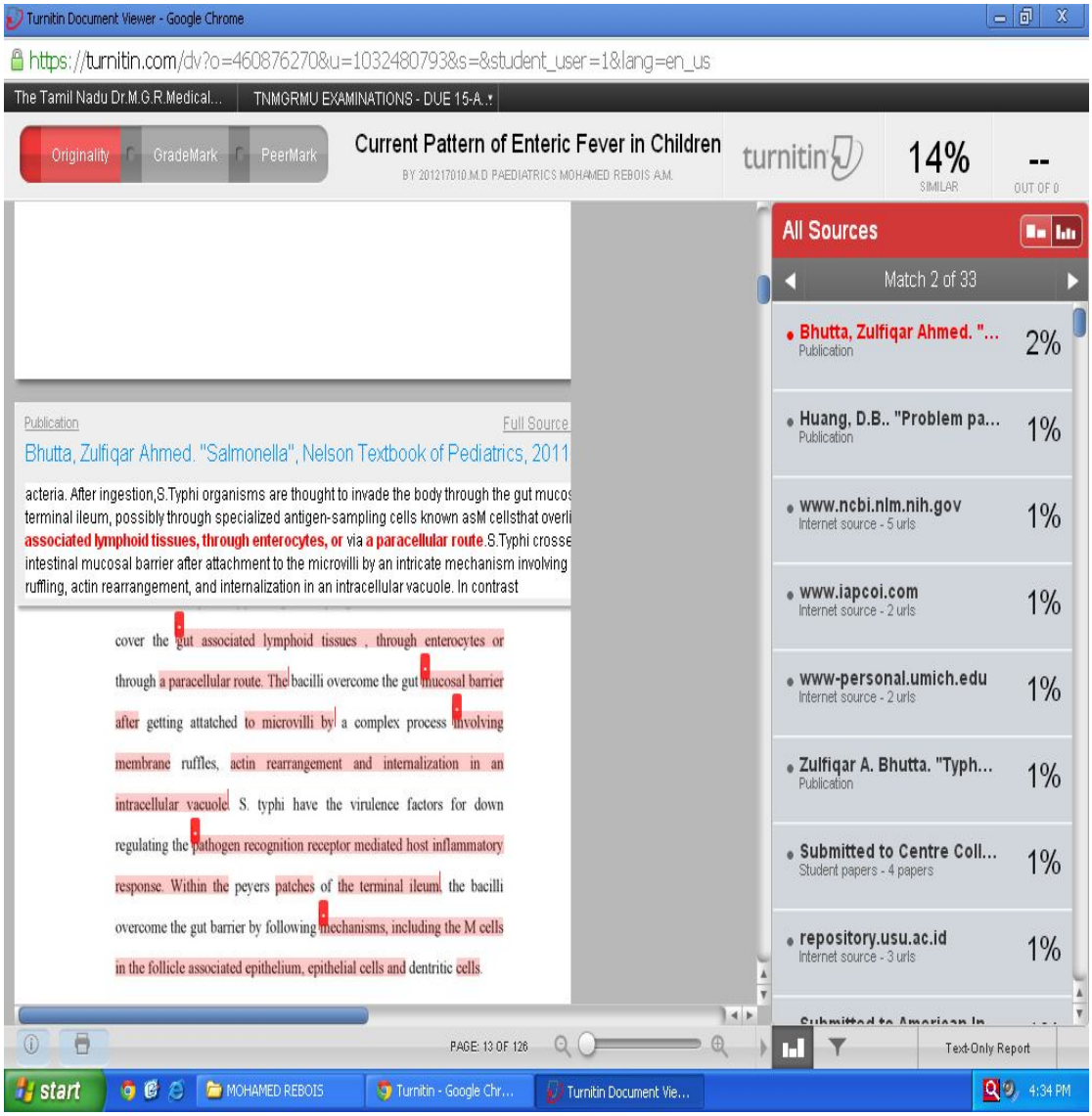
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acteria. After ingestion,S.Typhi organisms are thought to invade the body through the gut mucos
terminal ileum, possibly through specialized antigen-sampling cells known asM cellsthat overli
associated lymphoid tissues, through enterocytes, or via a paracellular route.S.Typhi crosse
intestinal mucosal barrier after attachment to the microvilli by an intricate mechanism involving
ruffling, actin rearrangement, and internalization in an intracellular vacuole. In contrast
cover the gut associated lymphoid tissues , through enterocytes or
through a paracellular route. The bacilli overcome the gut mucosal barrier
after getting attatched to microvilli by a complex process involving
membrane ruffles, actin rearrangement and internalization in an
intracellular vacuole. S. typhi have the virulence factors for down
regulating the pathogen recognition receptor mediated host inflammatory
response. Within the peyers patches of the terminal ileum, the bacilli
overcome the gut barrier by following mechanisms, including the M cells
in the follicle associated epithelium, epithelial cells and dentritic cells.
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INTRODUCTION

Enteric fever is a potentially fatal multisystemic disease due to the causative organism Salmonella enterica serovar typhi (S.Typhi). A related but milder disease is caused by S.Paratyphi A and less frequently by S. Paratyphi B and S. Paratyphi C. The term enteric fever comprises both typhoid and paratyphoid fever. Enteric fever represents as a main public health problem of the paediatric age group in developing countries and causes significant morbidity and mortality in spite of tremendous advances in the fields of pharmacology, microbiology and preventive medicine.

The extensive distribution of the organism in the ecology, its emergent prevalence in the global food chain, virulence and adapting capabilities results in enormous economical, medical, public health impact worldwide.

Without delay in treatment and proper antibiotic drugs, typhoid fever is usually a short term febrile illness. Treated it has few enduring consequences and a 0.2% death rate. If left untreated it is a life threatening disease of many weeks duration with long term morbidities. Increasing prevalence of antibacterial resistance and need for hospitalization are other problems associated with enteric fever.

CONTENTS

ABBREVIATIONS

WHO	-	World Health Organisation
S. Typhi	-	Salmonella enteric serovar Typhi
FQ	-	Fluoroquinolones
MDR	-	Multi Drug Resistant
NARST	-	Nalidixic Acid Resistant Salmonella Typhi
PS	-	Peripheral Smear
MP	-	Malarial Parasite
CNS	-	Central Nervous System

ABSTRACT

Background

Typhoid fever is a prevalent disease among paediatric population, and it leads to a diagnostic dilemma whenever a child presents with acute febrile illness. Rapid, simple and reliable diagnostic tests for typhoid fever is a long felt need for pediatricians. The typhidot assay is a recently available rapid serological diagnostic test for the diagnosis of typhoid fever.

Aim and Objectives

This study was conducted to find the reliability of typhidot assay over widal test in comparison to gold standard blood culture method, and also to find antibiotic sensitivity pattern of causative organism, clinical features of typhoid fever.

Material and Methods

A total of 167 children with clinical suspicion of typhoid fever enrolled in the study and a detailed clinical examination, routine laboratory investigation for fever workup and typhidot assay, widal test and sample for

blood culture taken. Patients were observed for clinical outcome and laboratory features.

Observations

26 children had positive blood culture. The sensitivity, specificity, positive predictive value and negative predictive value of the typhidot assay 88.46%, 81.56%, 46.94% and 97.46% respectively. The typhidot assay was found to be more reliable than widal test to diagnose typhoid fever.

Conclusion

The typhidot assay can be used as a suitable alternative to widal test in regions were facilities for culturing the blood is not available to diagnose the typhoid fever. The 3rd generation cephalosporin Ceftriaxone is suitable for empirical first line theraphy than Ciprofloxacin as there is a increasing trend in NARST.

Key words : typhoid fever, typhidot assay, widal test, sensitivity.

INTRODUCTION

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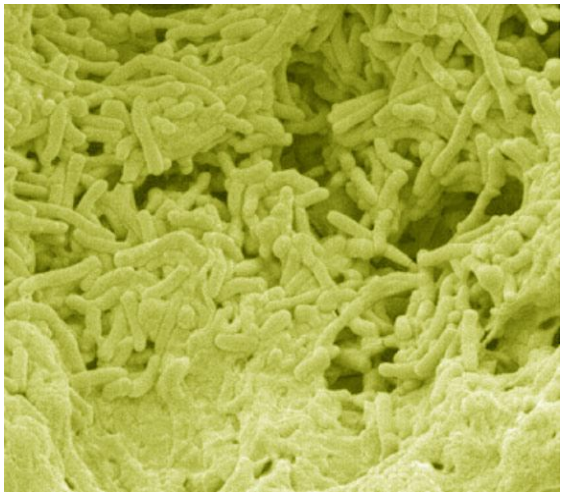
ORGANISM

S.Typhi is a highly human specific organism. It evolved 15000 to 50000 years ago and has highly adapted remarkable mechanisms for persistence in its human host[37]. It has no other natural host. S. typhi share many genes with Escherichia coli and at least 95% with S. typhimurium, many typical clusters of gene called as “pathogenicity islands” and related genetic materials have been obtained in the process of evolution. The paucity of single genes, gaining or loss of single genes or large islands of DNA fragments led to adaptation and restriction S. typhi to humans[1].



(Salmonella typhi growing over gall stones)

The name salmonella appeared after the pathologist D.E. salmon, who first isolated the S. Cholerasuis from pork intestine. The genus salmonella is classified into two species, each with multiple subspecies

and serotypes. The two species of salmonella is a genus of family Enterobacteriaceae. The two species of salmonella were salmonella enterica and salmonella bongori. The difference between two is SPI-2 (salmonella pathogenicity island) that is absent in S.bongori serotypes.

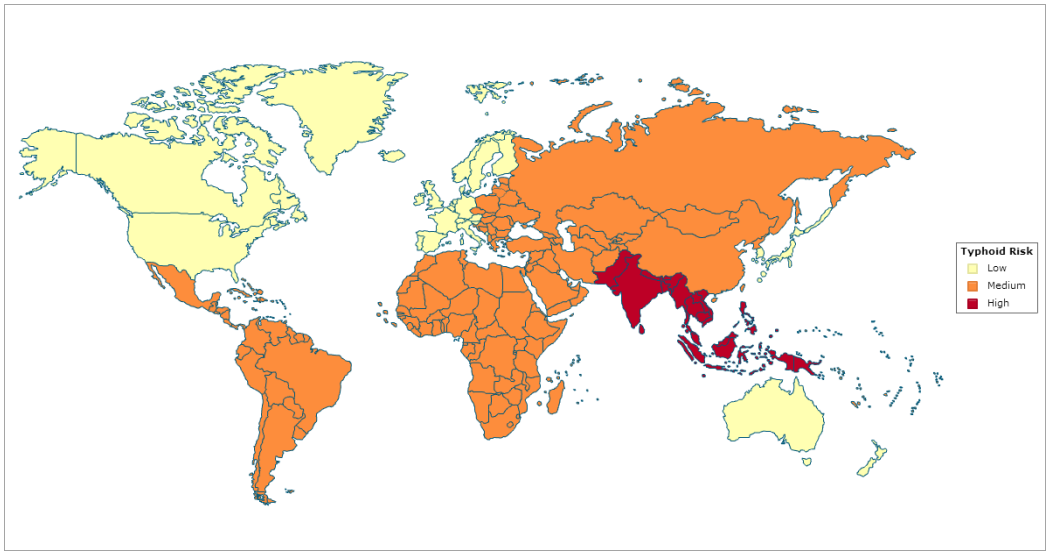
As per current salmonella nomenclature system in use at U.S. centres for Disease control and prevention and W.H.O. laboratories the full taxonomic designation Salmonella enterica subspecies enterica serotype Typhi can be minimized to Salmonella serotype Typhi or Salmonella Typhi[3].

Depending upon the recognition of formula for structures of O and H antigens by agglutinating techniques Salmonella are classified in kauffman-white scheme. A total of 2555 serovars defined in this system. Since L. Le minor explained most of the known serovars this is redesignated as White-Kauffman- Le minor scheme.

EPIDEMIOLOGY

Typhoid fever occurs all over the world, mostly in developing countries where environmental sanitation is poor. Endemicity is observed in Asia , Africa , Latin America , the Caribbean and Oceania , but 80% of total typhoid fever cases were from Bangladesh, china, India , Indonesia , Laos , Nepal, Pakistan and Vietnam[4]. Typhoid fever infects

approximately 21.6 million people (incidence of 3.6 /thousand populations) and kills approximately 200,000 people annually. Incidence varies in developing countries, ranging from 100 to 1000 /100,000 population.



(World map showing prevalence of typhoid fever. India comes under high prevalence region.)

The public health burden of typhoid fever in India is massive. Population based study done in New Delhi estimated the incidence of typhoid fever as 2730 per 1 lakh population in the age group of 0-4 years, 1170 per 1 lakh in the age group in 5-19 years , 110 per 1 lakh population in 20-40 years age group. Overall incidence of typhoid fever varies between 266 to 980 per 100,000 person years.

Typhoid fever incidence higher in school going children and young adults. Highest incidence is seen in those aged below 15 years and is

considerable even between ages of 1 to 5 years. It has no racial predilection.

HABITAT

Salmonella typhi is primarily an intestinal pathogen of human gastro intestinal tract. It is found often in sewage, river and in soil in which S.Typhi do not multiply considerably. It has been recovered from foods such as vegetables and fruits and are main contaminants of animal protein-feed supplements. It is capable of thriving in hostile environments such as ice, dust, clothes and water[38].

PHENOTYPE

Salmonella typhi is a gram negative rod , non spore forming, non capsulated, aerobic but facultatively anaerobic bacilli and measures about 2 to 3 by 0.4 to 0.6 microns in size.It is motile as a result of peritrichous flagella[38].

RESISTANCE

S.Typhi resistant to certain chemicals (sodium tetrathionate and brilliant green) that restrains other bacteria so it will be useful to incorporate them in culture media to recover S.Typhi from faeces. It will survive in sewage water for weeks, in ice for months, in soil for years under suitable conditions. It can be killed by heating to 54.4^0 C for 1

hour, 60^0 C for $1/4^{th}$ hour. S.typhi can be killed by boiling and chlorinating the drinking water. It is readily killed by 5% phenol within 5 minutes. Recent studies revealed various genes (Pho P/Pho Q, Omp R, env Z) responsible for the ability of S. typhi to adapt in environmental changes such as changes in pH, osmolality, changes in calcium concentration and to withstand effects of microbicidal proteins such as defensins present in the phagosomes of the phagolytic cells. The S. typhi can acquire R plasmids which enable them to develop resistance against chloramphenicol, amoxycillin, cotrimoxazole.

STRUCTURE OF ANTIGENS

The following antigens were used to describe the serological characteristics of S. typhi.

1. The O antigens, heat stable polysaccharides which makes a portion of cell wall lipo polysaccharide . This is determined by slide agglutination test. This is less immunogenic than the H antigen, hence produces titres less than H antigen following immunisation or infection. When mixed with antisera it produce compacted, chalky, granular clumps.

2. The H antigens are heat labile proteins of the flagella which have diphasic variation. It is determined by the tube agglutination test. The H

antigen is responsible for strong immunogenic response by S. typhi, provoke antibody formation quickly and in high titres following infection and vaccination. When mixed with antisera rapidly produces large, loose and fluffy clumps[39].

3. Surface Vi antigen

Vi ANTIGEN

Vi is a capsular polysaccharide of alpha-(1-4) linked N-acetyl-D-galactoseaminouronic acid randomly acetylated at C2/C3 positions. It protects from immune serum mediated killing, is anti-phagocytic and responsible for resistance to peroxide radicals. The virulence to the S.typhi is provided by the Vi surface antigen. Vaccines for typhoid fever targets this Vi antigen[39].

Vi surface antigen has no inherent virulence mechanisms, but offers virulence by disguising the oligosaccharide O antigen from immunological mediated attacks. It acts by coating the surface of the organism, thus avoiding antibacterial and opsonin effect of the O antibody. Being poorly immunogenic, allows only low titre antibody production following infection. Detection of Vi antibody is not helpful to diagnose the typhoid fever. Persistence of Vi antibody points toward carrier state.

CULTURE CHARACTERS AND GROWTH REQUIREMENTS

S.Typhi grow within temperature range from 7-48 degree celcius and pH ranging from 4-8. It multiplies at 43^0 C in an enrichment medium like bismuth-sulphite medium. Wilson Blair is a suitable selective media for S. typhi[39].

Blood agar: On blood agar, S.typhi and S.paratyphi usually forms non-hemolytic smooth white colonies.

MacConkey agar: On MacConkeyagar , it produces lactose non-fermenting smooth colonies. Colonies will have a distinctive vine leaf pattern.

Salmonella-Shigella agar: On SS agar S. typhi forms lactose non-fermenting colonies with black centre.

Desoxycholate agar: as in SS agar, it forms lactose non fermenting colonies with black centre.

Xylose-lysine-desoxycholateagar: On Xylose-lysine-desoxycholate agar, S. typhi forms transparent red colonies with black centre.

Hektoen enteric agar: On hektoen enteric agar, S. typhi will form transparent green colonies with black centre[38].

BIOCHEMICAL CHARACTERISTICS

1. S. Typhi does not produce gas on sugar fermentation with glucose, maltose, Mannitol and Sorbitol but produces only acid.
2. Lack of fermentation with sucrose, lactose, salicin and adonitol.
3. On cytochrome oxidase test it gives negative result.
4. Gives positive test on catalase reaction.
5. Reduces nitrates to nitrites in nitrite reduction test.
6. On Phenylalanine deaminase test fail to deaminate Phenylalanine.
7. Indole negative.
8. Produces positive reaction on methyl red test.
9. Acetoin not produced with vogue proskaeur test.
10. It does not produce urease.
11. Citrate not utilized when reacting with simmons citrate.

TRANSMISSION

Enteric fever principally spreads through faeco-oral route by ingestion of food or water contaminated with faeces. Transmission can occur directly through soiled hands contaminated with faeces or urine of cases or carriers or indirectly through contaminated water, milk, food and also through flies[40].

SOURCE OF INFECTION

Humans are the only natural host and reservoir for S. typhi. It is either patient or carriers. The infectious dose ranges between 10^3 and 10^6 organism taken orally[1].

Cases: cases may be mild, missed, or severe. A case or carrier is infectious until he excrete the organism in urine or faeces[40].

Carriers: They can be temporary (convalescent or incubatory) or chronic. Patients will excrete the bacilli in urine or stool for about a month[40].

Convalescent carriers –Patient will excrete the S.typhi for 6-8 weeks after which the number of bacilli in stool declines. By the end of 3rd month only 4% of patient will excrete the bacilli. At the end of 1 year average carrier rate is around 3%[39].

Chronic carriers –This state is defined as seepage of organism in urine or stools for more than a year.1% to 5% of enteric fever patients will become carriers. Risk factors were female sex, age more than 50 years, presence of gall stones, schistosomiasis, carcinoma of the gall bladder and other GIT cancers. Generally bacilli persists in the gall bladder or biliary tract. Carriers may excrete the organism for several years as long as 50 years. The famous typhoid Mary is a well known example for chronic carrier. She was presumed to have infected 53 persons, 3 of them died due to enteric fever, over the course of her carrier as a chef in hotel. She was isolated for nearly 30 years by U.S. public health department.

(Typhoid Mary in a 1909 newspaper illustration. Note the skulls she casts into the skillet)

RISK FACTORS FOR INFECTION

The S.Typhi could continue to exist for days in ground water, pond water and sea water, for months in contaminated eggs and oysters. Well-known risk factors were contaminated water supply, ice cream, flavoured ice drinks, food from street vendors, raw fruits and vegetables grown in fields fertilized with sewage.

Other risk factors includes a history of contact with enteric fever cases, poor hygiene, poor housing, over crowding, infection with H.pylori, open air defecation and urination and neglected food hygiene. Consequently typhoid fever incidence can be considered as an measure of general sanitation in any country[28].

INCUBATION PERIOD

This is generally 7-14 days but varies between 3-30 days[1]. It primarily depends on infecting dose. Hosts health and immune status also influence incubation period. The inoculam volume and type of vehicle with which bacilli ingested influence the attack rate and incubation period[1].

IMMUNITY

Antibody production can be induced by infection or vaccination. Large amount of antibody to somatic antigen O is formed as a reaction to infection in contrast to flagellar H antigen. Likewise large amount of antibody to flagellar antigen H is formed as a reaction to immunization in contrast to somatic O antigen. Antibodies to somatic antigen O or flagellar H antigen are not primary defence mechanisms. Since S.typhi is an intracellular organism cell mediated immunity had a major role in immunity. An attack does not produce permanent immunity. Re-infction may occur if large amount of bacilli ingested again. Gastric acidity and local intestinal immunity are main defence mechanisms to lower the susceptibility to infection. Specific IgD and IgA antibodies had been identified in intestinal local mileu of infected persons[39].

PATHOGENESIS[1]

After being ingested, the bacilli enters into intestinal cells by attach themselves to special type antigen sampling cells, called as M cells that cover the gut associated lymphoid tissues , through enterocytes or through a paracellular route. The bacilli overcome the gut mucosal barrier after getting attatched to microvilli by a complex process involving membrane ruffles, actin rearrangement and internalization in an intracellular vacuole. S. typhi have the virulence factors for down regulating the pathogen recognition receptor mediated host inflammatory response. Within the peyers patches of the terminal ileum, the bacilli overcome the gut barrier by following mechanisms, including the M cells in the follicle associated epithelium, epithelial cells and dentritic cells[1].

Immediately after contacting the epithelium, organism gather the TTSS-1. Then it translocates effectors into cytoplasm of enterocyte. This effectors can stimulate the host Rho guanosinetriphosphatases (GTPases) leading to actin cytoskeleton reorganization and membrane ruffling. The effectors also induces mitogen activated protein kinase (MAPK) pathways and destablization of the tight junctions[1]. The uptake is facilitated by modifications in the actin cytoskeleton brought by actin binding proteins Sip A and Sip C. The destabilization of tight junctions leads to transmigration of neutrophils from the basolateral surface to

apical surface, paracellular fluid leakage, movement of bacteria to basolateral surface. It is followed by internalisation organism by macropinocytosis, enclosed in a large phagosome which is created of membrane ruffles. Then this phagosome fuses with lysosomes, acidifies and shrinks to form a adherent membrane around the S.typhi, thus completes the making of Salmonella containing vacuole (SCV). TTSS-2 initiation leads to translocation of effector proteins (Sif A, PipB2) necessary for Salmonellae induced filament (Sif) formation by the side of microtubules.

After crossing the intestinal mucosa, S. typhi go into in to the mesenteric lymph nodes and enter into the bloodstream via the lymphatics (through thoracic duct).This primary bacteremia is asymptomatic. The blood-borne bacteria were disseminated throughout the body. They colonize the organs of RES, in which they replicate within macrophages. Thus within 24 hours of entry, S.typhi begins its replication in an intracellular mileu of reticuloendothelial system organs like spleen, liver, bone marrow etc. After replication, i.e. incubation period, organism are released back into the blood, leading to secondary bacteremia marking the commencement of symptoms. This secondary bacteremia is a sustained one and having 1-10 bacteria per ml of blood.

The capability of S. Typhi to survive within macrophages after phagocytosis is an significant virulence factor to set up systemic infection. This trait encoded by the PhoP regulon in the genome of S.typhi. The TTSS-2 and the surface Vi polysaccharide capsular antigen were the important virulence factors of the organism to cause systemic infection. Later one prevents the binding of C3 to the surface of bacterium, thus interfering with phagocytosis.

TABLE 1 : FACTORS RESPONSIBLE FOR SUSCEPTIBILITY TO S. TYPHI INFECTION [41]

Sickle cell anemia	Reticuloendothelial system overload owing to hemolysis, Functional asplenia, Tissue infarcts Defective opsonization.
Neutropenia (congenital or acquired)	Polymorphonuclear neutrophils needed for killing
Chronic Granulomatous disease	Defective killing by polymorphonuclear neutrophils
AIDS	Low CD4 Effects of Malnutrition on cell mediated immunity Survival of organism in macrophages (owing to salmonella genes PhoP/PhoQ, spvA-D,R)
Organ transplantation , immunosuppression	Defective cell mediated immunity
Gastrectomy	Loss of stomach acid barrier
Malaria	Reticulo endothelial system overload owing to hemolysis Abnormal complement levels Abnormal macrophage function
Bartonellosis	Reticulo endothelial system overload owing to hemolysis
Schistosomiosis	Salmonella sequestered in schistosomes protected from host defenses and antibiotics

TABLE 2 : PUTATIVE PATHO PHYSIOLOGICAL BASIS OF SELECTED CLINICAL FEATURES OF S. TYPHI INFECTION[41]

Disease manifestation	Mechanism and bacterial genes
Bloody diarrhea	sip A-D mediated invasion and intereukin 8 mediated inflammation
Watery Diarrhea	stn enterotoxin (cholera like toxin) SopB- mediated intestinal inflammation and fluid secretion Serotype that induce transepithelial polymorphonuclear lecocyte migration are more likely to cause diarrhea than are serotypes that do not.
Bacteremia	ViaB (Vi synthesis) Capsular antigen interferes with C3 binding, rck resistance to serum complement (virulence plasmid encoded) rfb encodes lipopolysaccharides synthesis , lipopolysaccharide contributes to persistence of bacteremia
Relapses , prolonged fever , failure of certain antibiotics	Survival in macrophages (sseABC, spiC, mgtCB , cyototoxin and virulence plasmid genes spvRABCD)

PATHOLOGICAL CHANGES

Typhoid fever is primarily an infection of hematopoietic system. The mononuclear cell hyperplacia is the important microscopic feature. Typhoid nodules are characteristic. It leads to lymphadenopathy, splenomegaly and enlargement of lymphoid tissues in the intestine especially the terminal ileum (peyers patch). The mononuclear hyperplacia may also be observed in bonemarrow, liver and lung[38].

CHANGES IN THE INTESTINE

Peyers patches are lymphoid aggregates seen in the terminal regions of small intestine. Payers patches are invaded by the organism, during primary inestinal infection or during secondary bacteremia, further seedling occurs through infected bile. This leads to hyperplacia and infiltration with chronic inflammatory cells later necrosis of superficial cells resulting in development of irregular, ovoid ulcers along the long axis of intestine so that stricture will not form when healing occurs. When underlying blood vessels eroded by this ulcer, it may lead to severe bleeding. A transmural perforation may lead to peritonitis. This ulcers are very shallower in children than in adults. So, both bleeding (<1%) and perforation (0.5 to 1%) are rare in children.

The lymphoid follicles in the caecum, jejunum, proximal colon and appendix also get involved resulting in swelling and hyperemia of this lymphoid organs. The main feature in all these lesions is lack of polymorphonuclear leucocyte invasion. Inflammation, increase in sinusoids and enlargement also seen in mesenteric lymph nodes.

CHANGES IN THE LIVER[42]

Liver becomes enlarged and swollen. There are areas of focal necrosis resulting in tiny nodules. Histopathology of liver shows typhoid

nodules, cloudy swelling, ballooning degeneration, moderate fatty change and macrophages in the sinusoids. In addition, intact S. typhi bacilli have been demonstrated in the parenchyma of the liver by doing immuno histochemistry and have been cultured from liver biopsy. The liver lesions seen microscopically mimics the picture of acute viral hepatitis.

CHANGES IN GALL BLADDER

The infected bile render the stool culture positive. Acute cholecystitis occurs rarely. Preexisting gallbladder disease leads to chronic infection, resulting in chronic fecal carriage. Chronic cholecystitis and gall stones are frequent associations with carrier state. In vast majority of cases, infection of the bile terminates spontaneously during convalescence peroid.

CHANGES IN THE SPLEEN

Proliferation of splenic cells, of splenic sinusoids and pulp results in soft enlargement of spleen. Capsule also becomes tense. Focal areas of necrosis can be seen microscopically. Rapid enlargement can results in rupture and splenic hemorrhage. Splenic abscesses are observed occasionally.

RESPIRATORY SYSTEM

Bronchitis is the commenest form of respiratory tract involvement[1]. Rarely lobar pneumonia, empyema, pleurisy were observed.

CHANGES IN BONE MARROW

The lesions in the bonemarrow contains large number of phagocytic cells which are derived from histiocytic members of reticuloendothelial system[34]. They result in leucopenia, which is more common in adults than in children. Children frequently have leucocytosis. Bone marrow culture is gold standard for diagnosing typhoid fever. They increses the yield in detection of S.Typhi.

CENTRAL NERVOUS SYSTEM CHANGES

Neurological involvement is relatively infrequent in children. The word typhos in Greek language means smoke. It is said to indicate the clouding of consciousness associated with fever. Encephalopathy, meningitis, intracerebral hemorrhage and spinal cord involvement can occur[36].

CHANGES IN THE KIDNEYS

Clumps of organism can be seen in the glomeruli as well as in urine microscopically. Immune complex glomerulonephritis also have been reported in literature.

CHANGES IN THE HEART

Subacute bacterial endocarditis may occur in patients with preexisting valvular heart disease. Arrythmias, sinoatrial block can occur. The relative bradycardia, i.e. lower pulse rate out of proportion to fever is uncommon in children. It is due to effect of toxins on the myocardium.

CHANGES IN THE BONE

Bone can be involved in the form of periosteitis and osteomyelitis. Periosteitis is common in tibia and ribs. Bone abscesse seen infrequently.

CHANGES IN THE MUSCLE

Zenkers degeneration (waxy degeneration) can be seen in muscles. Frequently involved muscles are the diaphragm, rectus abdominis and the intercostals and thigh muscles.

CHANGES IN THE SKIN

Rose spots can be seen in skin, which are due to bacterial embolisation. Rose spot culture is also a diagnostic tool, their culture may be positive. They are not only for typhoid fever, can also be seen in infections with shigella and non typhoidal salmonellosis.

CLINICAL FEATURES

The clinical features fever may vary depending on the age of the patient.. The clinical spectrum ramnges from a mild febrile illness with low grade fever, malaise, and dry cough to a lethal disease due to

multiple complications. The severity and outcome of the infection depends on the duration of the fever before starting treatment, antimicrobial agent used, age of the patient, previous exposure, immunization status, virulence of the strain, size of the inoculam ingested, immune status, HLA type and history of concomitant drug intake like H2 receptor blockers. People living with HIV and AIDS are at increased risk for typhoid fever. World Health organization classifies presentation of typhoid fever into three categories, acute non complicated disease, complicated typhoid fever and carrier state.

ACUTE NON COMPLICATED DISEASE

Protracted fever, diarrhoea, headache, malaise, loss of appetite characterizes the acute non complicated disease. Dry cough due to bronchitis is common in early stages[3].

COMPLICATED DISEASE

Typhoid fever can be a severe disease in upto 10% of patients. Presence of occult blood in stool can be seen in 10-20% of patients 3% may have melena. This group also comprises GI perforation, peritonitis, hepatitis, toxic myocarditis, DIC, neurological sequelae like delirium, Gullain-Barre syndrome. They are described in detail below[3].

CARRIER STATE

This state develops in 1-5% of patients. Mostly they harbor the bacilli in their gallbladder. The chronic carrier state is defined as persistence of S.typhi in urine or faeces for a period > 3 months in children. The risk for chronic carrier state in children is low (less than 2% for all infected children) and increasing with age. A chronic urinary carrier state is observed with coexisting urinary bladder infection of schistosoma hematobium. Serology for the Vi antigen differentiates chronic carrier state from acute infection with S. typhi, as chronic carriers have the high level of antibodies against this antigen.

SYMPTOMS AND SIGNS

Enteric fever presents as high grade fever with different features like myalgia, abdominal pain, hepatomegaly, splenomegaly and loss of appetite. Children can have the loose stools in early stage and may be followed by constipation. It is difficult to differentiate the typhoid fever from other endemic infections like malaria, dengue fever, leptospirosis and acute viral hepatitis in the early stages of typhoid fever.

Typhoid fever may present atypically where malaria and schistosomiosis were endemic. The multidrug-resistant S.typhi infection is more severe than chloramphenicol sensitive typhoid in terms of higher

toxicity, complications, and case fatality rate, because of greater virulence and increased numbers of circulating organisms. Nalidixic acid resistant and fluoroquinolone resistant strains are associated with more morbidity and treatment failure[1].

Classical step-ladder pattern of typhoid fever is increase in the temperature by about 2^0 F during evening times and falls about 1^0 F during morning times, so that at the end of 5 days reaching a plateu of between 102 and 104 ^{0}F above which it rarely ascends. But this step-ladder pattern is rare in children. There are studies showing 60% patients had continuous fever and rest had intermittent, remittent or irregular fever. Fever is frequently associated with frontal headache. Relative bradycardia or pulse temperature dissociation is rare in children.

Malaise is a typical presenting symptom in typhoid fever. Chills is another characteristic symptom but rigors are uncommon.

Headache is persistent rather than severe. Occasionally headache may severe enough to suggest meningitis. Myalgia and arthralgia are common. Abdominal pain may be so severe so as to mimic acute appendicitis.

Many patients presents with cough and during the first week of illness it closely resembles acute bronchitis. Generally the appetite is

poor. Diarrhoea is a common symptom in early presentation. “Pea soup diarrhoa” occurs during the third week of fever and it contains the red blood cells, not the frank blood. Severe diarrhoea has been reported in HIV patients with typhoid. Alternatively constipation can be seen during first week, but it is more common in adults. Presence of constipation is associated with higher relapse rate.

Tongue becomes coated with white or brown coating which spares the tip and edges and may have musty damp-hay like odour[41]. Rose spots are salmon coloured macular or maculo-papular exanthem which may appear in crops around 7^{th} to 10^{th} day of fever. Their number is around 10-15, visible on the lower chest and abdomen and lasts around 2-3 days then gradually disappear leaving a brownish stain. Often they are only 4 or 5 spots, more than 20 spots is regarded as profuse rash. They disappear on pressure, ranging in diameter of 2-4 mm and not easy to observe in dark skinned children[1].

Around the 7^{th} to 10^{th} day of fever a soft splenomegaly can be noticed. The splenomegaly is mild, just palpable or upto 3 cm below the left costal margin. Hepatomegaly may be detected as early as first week, but commonly during the second and third weeks of fever and took several weeks to disappear. Jaundice is noted in around 16% of patients.

By the end of 2nd week the patient will become profoundly ill, unless the course is modified by antibiotics. During the 3rd week increase in toxemia, hepatosplenomegaly, intestinal bleeding, perforation due to ileocaecal lymphatic hyperplacia of the peyers patches may occur, together with secondary bacteremia and peritonitis. Septic shock or an altered level of consciousness may develop. patient may become comatous and die. In the absence of acute complications or death from overwhelming gram negative sepsis, symptoms gradually resolve over weeks to months.

“Coma vigil” or muttering delirium is state where the patient is not unconscious but not conscious of anything, confused, sleepless and disoriented. The patient lies in the bed with open eyes but oblivious of surroundings. This state can be seen if the patient was not treated properly and when he reaches the third week.

The face may reflect profound toxemia and becomes expressionless, shunken, shallow and a flush over the cheek bones that will spread as the illness worsens. The famous clinicians Louis and Osler described the appearance typhoid fever patient during the advanced stage of the disease as follows;”muttering delirium, twitching of fingers and wrists (sub sultustendium), agitated, plucking at the bed clothes (carphology), staring, unarousable stupor (coma vigil).

Following recovery, up to 5% of patients become chronic carriers. The mortality rate is less than 1% if correct treatment is given. It is around 20-30%, if not treated. The most important reason for poor outcome is almost certainly a delay in starting antibiotic treatment.

Relapse rate in typhoid fever is usually around 2 to 4%.Inspite of this high relapse rate, reasons for relapse is largely unknown. Relapse is said to be present with the recurrence of clinical signs and symptoms, culture proven infection with S. typhi, with an antibiogram identical to the original isolates, within 8 weeks of cessation of successful treatment of initial infection. Relapses typically occur 2 to 3 weeks after the defervescence of fever and milder than the previous illness. The early use of effective antibiotics may be the cause for increase in relapse presumably because early appropriate antibiotic treatment prevents the development of adequate immune response.

Typhoid fever varies in its clinical course. Variations in the classic theme includes[41]

1. A completely afebrile course can be seen in debilitated children
2. High spiking fever from the first day of fever (particularly in younger children)
3. A focal presentation (e.g. pneumonia, nephritis)
4. A severe course during relapses.

Typhoid fever has the following differences in the clinical picture when presenting in young children than older children.

- Respiratory symptoms and signs are seen more often
- Diarrhoea is frequent in young children, whereas constipation is more often seen in older children.
- Relative bradycardia is unusual in young children.
- Perforation is less common in young children.
- Leucopenia may not always occur.

The differential diagnosis of typhoid fever includes Dengue fever, leptospirosis, acute viral hepatitis, acute viral fever, ricketsiosis.

COMPLICATIONS OF TYPHOID FEVER

Since typhoid fever is a multisystem disease, complications have been reported in every system of the body. Complications occur in 10 to 15 % of patients. Most of them develop during second or third week of fever.

GASTROINTESTINAL COMPLICATIONS

The most common complications of typhoid fever are related to gastrointestinal tract. Paralytic ileus and abdominal distension being the most frequent manifestations in GIT. The intestinal perforation and severe gastrointestinal hemorrhage are the another two most dreaded complications[8].

1. INTESTINAL HEMORRHAGE

During the first week itself, there may be evidence for hemorrhage. Occult blood in stools is detected in 10-20% of patients, 3% have melena. During the second to fourth week of illness, in less than 1% of children severe hemorrhage can result from erosion of blood vessels in the peyers patches due to ulceration. When the amount of hemorrhage is greater, there will be a thready pulse, signs of collapse[1]. The incidence of hemorrhage is more than perforation. Hemorrhage generally occurs from multiple, variable sized punched out ulcers in the distal ileum and proximal colon. It is infrequent in children.

2. INTESTINAL PERFORATION

The perforation has been reported in up to 0.5 to 1% of hospitalized patients. This also rare in children and usually occurs during second to fourth week of illness. Perforation may be preceded by marked increase in abdominal pain (usually in the right lower quadrant), tenderness, vomiting and signs of peritonitis. A rapid decline in temperature late in the illness should arouse suspicion of perforation; such a decline in temperature classically followed by an increase a few hours later as peritonitis develops[3].

Intestinal perforation and peritonitis are accompanied by tachycardia, hypotension, abdominal tenderness and guarding and ensuing abdominal rigidity, absence of bowel sounds, loss of liver dullness .A rising WBC count with a left sided shift and pneumoperitoneum on abdominal X ray erect view, were frequent findings.

The perforation size may range from pinpoint to several centimeters, mostly occur at the lower end of ileum. Gram negative sepsis may ensue. In three quarters of cases it is single perforation and associated with high mortality rate. Inadequate antibiotic treatment, male sex and leucopenia have been found to be independent risk factors for intestinal perforation.

3. PARALYTIC ILEUS

In typhoid fever abdomen may be tender, doghy in consistency and with slight guarding. Distension also may be a part of illness. But when it is greatly distended with tenderness and severe vomiting it indicates paralytic ileus or meteorism. Paralytic ileus is due to severe toxemia, severe intestinal lesions with or without peritonitis and hypokalemia.

HEPATIC COMPLICATIONS[11]

Abnormal liver function test is observed in many children with typhoid fever. Clinically significant hepatitis, jaundice and cholecystitis

are rare in children. The prevalence of hepatobiliary complications is between 1-26%.Risk factors were dwelling in endemic region, splenic trauma, HIV, hemoglobinopathy.

The presence the of jaundice in children with typhoid fever is associated with higher rates of mortality and morbidity. Jaundice is a rare presentation in enteric fever and if present it may lead to diagnostic problems, especially in the tropics where malaria and viral hepatitis are common. There are several reports that have been made about typhoid hepatitis. The incidence of jaundice in typhoid fever ranges between 4.8% and 17.6%. Jaundice usually manifests about 1 week from the onset of fever and improves slowly with recovery of illness. Jaundice can occur in the absence of liver enlargement. Jaundice mostly results from conjucated hyperbilirubinemia and it is due to hemolysis and impaired excretion as a result of canalicula occlusion by swollen hepatocytes. This impaired excretion followed by focal hepatocellular necrosis which leads to rupture of bile canaliculi resulting in direct reflux of bile into the hepatic sinusoids, hence the predominant elevation of conjucated bilirubin. Typhoid fever should be considered in any febrile child who develops jaundice about one week after the onset of fever with or without hepatomegaly.

Liver function test may show the hepatic dysfunction even in the absence of icterus. A significant rise in serum bilirubin without a parallel increase in serum ALT is unusual in viral hepatitis but a common finding in enteric fever. Elevated liver enzymes can be seen in 21 to 60% of cases. Mild elevation of serum transaminases (upto 3 times above the normal) can be noted in around 60% of typhoid fever children and is four times more common than moderate elevation (3-20 times above the normal). This biochemical evidence of liver dysfunction is due to invasion of S. Typhi in to liver and high concentration of toxins that damage the liver cells. The S.Typhi proliferates in the liver cells and leads to hepatic damage by stimulating the synthesis and release of cytokines.

GALL BLADDER

Gall bladder may be involved in the form of acute cholecystitis, but it is very rare. Involvement may range from mild catarrhal type to dangerous perforation of gall bladder, mostly occurs around the end of second week. Gall bladder may harbor the bacilli, leading to chronic carrier state.

CNS COMLICATIONS[36]

These are relatively rare in children. Neurological manifestations are associated with high case fatality rate. But usually the recovery is

associated with no permanent sequelae. Their prevalence is between 3 to 35%. Identified risk factors include living in the endemic region, malignancies, sinusitis, foci in the lung and osteomyelitis of the skull.

A wide variety of neuropsychiatric manifestations can occur and includes, delirium, psychosis, increased intracranial pressure, acute cerebellar ataxia, chorea, deafness, guillain-barre syndrome, meningism, meningitis, convulsions, encephalopathy, cerebral edema, subdural empyema, cerebral abscess, ventriculitis, transient parkinsonism and motor neuron disorders.

TYPHOID MENINGITIS

S. Typhi should be considered in the differential diagnosis of gram negative bacillary meningitis, in children of the endemic populations[29]. It is more common in young children, neurological symptoms and signs will not be apparent. Seizures and coma were the most frequent presentations. S.typhi can be recovered from cerebrospinal fluid. The main findings in the CSF biochemistry is increased leucocytes, increased proteins and low glucose determinations. The mononuclear cells will predominant than polymorphs. Thus CSF features might look like viral meningitis and can be distinguished by means of culture method.

HEMATOLOGICAL COMPLICATIONS

These include anemia, disseminated intravascular coagulation, leucopenia, eosinopenia, thrombocytopenia[35]. Other observed rare sequelae are fatal bone marrow necrosis, hemophagocytosis syndrome[1].

Anemia in typhoid fever may be due to blood loss from intestinal lesions or hemolysis or defective production of RBC in the bone marrow. The bone marrow histology reveals myeloid maturation arrest, decrease in the number of erythroblasts and megakaryocytes with increased phagocytic activity of histiocytes. Acute hemolytic anemia and hemoglobinuria have been reported. Patients who have thalassemia and glucose-6-phosphate dehydrogenase deficiency may have hemolysis during typhoid fever.

In younger children leukocytosis is frequent and may reach 20000 to 25000cells/mm^3.Thrombocytopenia may indicate a severe infection and usually accompanies the disseminated intravascular complication.

RESPIRATORY COMPLICATIONS

Respiratory symptoms of enteric fever, such as cough occur in 11 to 86% of patients. Pneumonia, empyema and bronchopleural fistulas seen in 1 to 6% of cases.A case of massive pulmonary embolism in the course of pneumonia of typhoid fever has been reported. Patients with

lung involvement of typhoid fever frequently have lung anamolies, prior history of lung infection, sickle cell anemia, and immune suppression due to HIV infection.

Patient may present with fever, chills, cough (with or without expectoration), pleurisy, coarse crackles and bronchial breathing on auscultation, diarrhoea and leucopenia. Chest X ray findings observed in 24% of children with features of bronchitis and pneumonia. S.typhi is very rarely isolated from the sputum[42].

When comparing to lobar pneumonia, brochopneumonia is more common in children. Sympathetic bilateral pleural effusion and pneumothorax have been reported. Pneumonia occurs in the second or third week of illness. Cases of acute respiratory distress syndrome (ARDS) have been reported and it is associated with very high mortality. Other complications are tonsillitis and pharyngitis.

CARDIOVASCULAR COMPLICATIONS

The prevalence of cardiovascular system involvement is between 1 to 5%. Most of the children with cardiac complications have underlying cardiac problems like preexisting valvular diseases, RHD and birth defects of heart. Cardiovascular complications may manifest as asymptomatic electrocardiographic changes, toxic myocarditis presenting

as arrythmias, sinoatrialblock, cardiogenic shock and infection of prosthetic valve.

Pericarditis and arteritis noted in < 1% of cases. Sustained bacteremia may result in an increased tendency for this organism to attach to endovascular compartments, including atherosclerotic aneurysms[42]. One study reveals cardiac arrythmias can occur in 3% of patients. ECG features has no are no diagnostic value and may reveal nodal tachycardia, A-V dissociation with narrow QRS complexes, and/or non specific ST segment changes. Echocardiogram might reveal vegetations. A transesophageal echocardiography has a greater sensitivity when comparing with a transthoracic 2 dimensional echocardiogram to identify the valvular dysfunctions and vegetations.

The incidence of toxic myocarditis is high with MDRST infection. Case report of venous thrombosis involving leg veins reported by J.B.Gosh from west bengal in a 9 year old girl.

MUSCULO SKELETAL COMPLICATIONS

Focal suppurative infection with S.typhi can occur almost anywhere. Most common sites are bone (particularly in sickle cell anemia) and central nervous system. Involvement of bone and joint in children is very rare, prevalence is less than 1% only. Risk factors include

type 1 diabetes, systemic lupus erythematosus, lymphoma, liver diseases and steroid use.

Osteomyelitis due to S. Typhi can result from one of the three mode of spread; blood borne spread, contiguous spread or as due to vascular insufficiency[42]. Of these, hematogenous spread is commonest. The sites commonly involved are the diaphysis of long bones such as the proximal humerus, distal femur and distal tibia. Less common sites includes the spine, the sternochondral junctions ,radius, ulna, sternum, ribs, sternoclavicular joints and cranium. Cases of septic arthritis have been reported. Patient may present with fever, swelling and arthralgia with or without effusion. Investigation may reveal elevated WBC count. Aspiration of the joint fluid is essential for diagnosis of S.typhi arthritis. A leucocytosis (>50000 lecocytes /ml) and lowered glucose (< 50% of the plasma glucose concentration) of the joint fluid indicates septic arthritis.

GENITOURINARY SYSTEM COMPLICATIONS

These complications are rare, even in endemic areas. Prevalence is less than 1%.Chronic urinary carriers can be seen in endemic areas. In areas where Schistosoma hematobium infection is endemic, this urinary carriers may have an active co- infection with schistosoma hematobium[39].

Predisposing factors include congenital anomalies, calculi or obstruction, pyelonephritis, dermoid cyst and renal transplant. In a case series report f 18 patients with urine culture confirmed infections, almost 80% of patient had symptoms of fever, dysuria, incresed frequency and suprapubicpain. Urine routine examination of these patients revealed the pyuria in 94% of patients and proteinuria in 91% of patients.The diagnosis is established by urine culture method, detection of 10^5 CFU per ml of urine.

Hemolytic –uremic syndrome, pyelonephritis, nephrotic syndrome, orchitis are other reported complications.

MISCELLANEOUS COMPLICATIONS

Rarely patient may develop immune complex glomerulo nephritis and irreversible loss of renal function has not been reported. One case of cutaneous vasculitis has been reported. Skin biopsy in this patient shown leucocytoclastic vasculitis with superficial and deep perivascular infiltrate of lymphocytes and neutrophils and C3 deposits in dermal vessels.

5 cases of haemophagocytosis has been reported in literature.These patients presented with fever, lymphadenopathy, hepatosplenomegaly, pancytopenia, coagulopathy, hepatitis, jaundice and hyperferritinemia. Bone marrow was hypocellular and reduced

megakaryocytes, myeloid precursors and erythroid precursors. A gram stain of bone marrow culture proving S.typhi infection is required for establishing the diagnosis of haemophagocytosis in typhoid fever.

Parotitis and parotic abscess cases due to S.typhi reported. Typhoid rhabdomyolysis with acute renal failure and pancreatitis has been reported from vietnam in a 15 year old male.

Yacaman-Handal et al from spain reported a case of acute pancreatitis in a pre- school child. Many cases of suppurative lymphadenitis and abscesses due to S.Typhi have been reported. Caksen et al described a case of 12 year old boy with splenic abscess and pleural effusion due to S.Typhi. Splenic abscess is very rare in typhoid fever.

LABORATORY DIAGNOSIS OF TYPHOID FEVER

Clinical diagnosis of typhoid fever is not easy, due to absence of specific clinical signs. The mainstay of diagnosis is isolation of S.Typhi from the blood or other specimens. Culture of the S. Typhi may be obtained from stool, urine, blood, bone marrow, bile and from rose spots. Of these culture of the bone marrow has the highest yield, particularly if the patient has been treated with antibiotics earlier. But bone marrow aspiration is tricky and invasive one.

Stool culture may be sometimes positive during the incubation period. During the first week of typhoid fever, approximately 40 to 60 percent of patients have positive blood and urine cultures. During the subsequent weeks , the yield of blood culture decreases as the yield of stool and urine culture increases. Culture of duodenal fluid aspirate obtained by string capsules can be as sensitive as culture of bone marrow aspirates.

CULTURE

Conventional blood culture makes the use of BHI broth or bile broth or biphasic media for recovery of S,typhi.For the optimum yield of the S.Typhi the quantity of blood to culture broth should be 1:10.This will dilute the antibacterial substances that are present in the blood[38].

Conventional blood culture bottles are incubated at 37°C aerobically. The tubes are examined daily for the growth (hemolysis, turbidity) during first 6 – 18 hours. Serial blind subcultures from BHI broth has to be done on Chocolate agar & Mac Conkey agar plates on alternative days till 7 days. The growth if any is identified by biochemical reactions and confirmed.

Clot culture

Clot is inoculated is inoculated into a broth medium contain streptokinase. This method increase the yield of culture positivity.

Buffy coat culture

About 5 ml of blood mixed with heparin , centrifuged. Then the buffy coat can be aspirated and inoculated into solid media straightly or after lysis with 0.1% digitonin. This process will be 100% sensitive and specific[39].

BONE MARROW CULTURE

This is the only bacterial infection of humans for which bone marrow aspiration is suggested customarily with sensitivity of more than ninety percent. High colony counts are there in the bone marrow when comparing to blood and unlike blood culture, are not affected by up to 5 days of prior antibiotic treatment.

BILE CULTURE

Bile is a suitable culture medium for S.typhi, so helpful to detect carrier state.

STOOL CULTURE

S.Typhi are excreted in stool all over the course of illness and even during convalescence. It is helpful to detect the carrier state. The organism can be isolated from the stools between the third and fifth week of the disease[39].

Stool culture can be done on plates of one or more types of selective media, both directly and after preliminary culture on a liquid enrichment medium. The most commonly used media were Selenite F broth, DCA, McConkey agar, XLD agar. Wilson and Blair's medium is also a suitable selective medium. When comparing to adults, children have increased incidence (sixty percent versus thirty percent) of stool culture positivity.

SEROLOGICAL TESTS

ANTIBODY DETECTION

WIDAL TEST

This test detects agglutinating antibodies to O and H antigens of S. Typhi and H antigens of S. Paratyphi A and B. This test becomes positive towards the end of the first week and reaches the highest point during the third week of illness. Antibody to O antigen are mainly Ig M type and increases in the beginning of disease. It disappears quickly. H antigens are flagellar antigens of the organism. Generally antibodies to O antigen appears on the day six to eight and antibodies to H antigen appears on days ten to twelve following the onset of the illness. This tests can be done in tubes or on slides[38].

The positive Widal test result means demonstration of rising titres of antibodies in paired sera taken at ten to fourteen days interval. Demonstration of rising antibody titres in a paired sera at on interval of seven days is diagnostic of the disease but is too late for taking clinical decision making. The test done using a single, acute phase serum sample is called as unpaired Widal test, it has lower sensitivity and specificity in countries were the enteric fever is endemic. The test results must be interpreted with caution in case of previous infection or immunization with typoid fever vaccine. The result may be affected due to cross reacting epitopes shared with other Enterobacteriaceae, that are present in the sample.

MODIFIED WIDAL TEST

This test helps to distinguish the recent infection from a past one. A positive Widal test may be due to Ig M or Ig G antibodies. In modified Widal test, the serum is mixed with 2-mercapto ethanol which can selectively inactivate the IgM and leads to decrease in the titres of Widal test. The decline in the titres of modified Widal test in contrast to customary Widal test points toward latest infection.

TYPHIDOT ASSAY

This is a dot-blot enzyme-linked immunosorbant assay which can detect specific IgM and IgG antibodies to a 50 kDa Outer Membrane

Protein of S. Typhi[7]. The test uses peroxidase labeled anti-IgM (Typhidot-IgM) or anti-IgG antibodies. The detection of IgM antibodies indicates the early phase of illness, whereas the detection of both IgG and IgM implies acute typhoid in the middle phase of infection[3].

Diagnostic usefulness of the Typhidot test was augmented by discriminatory recognition of IgM antibodies. The modified test Typhidot-M, which allows inactivation of IgG permits the contact of the antigen to the specific IgM. The test is easy, quick, ninety five percent sensitive, seventy five percent specific and has high negative and positive predictive values. In a study carried out in Vellore, the Typhidot test conferred a sensitivity of hundred percent and specificity of eighty per cent.

IGM DIPSTICK TEST

The typhoid IgM dipstick assay deects of S.Typhi-specific IgM antibodies in serum or whole blood samples[3].

ANTIGEN DETECTION

Rapid latex agglutination- Detects specific antigens in culture supernatants. The method is highly sensitive and specific almost paralleling blood culture.

Co- agglutination test : It is a slide agglutination method uses killed Staphylococci (Cowan I strain) having protein A which binds with Fc fragment of IgG specific against somatic O antigen of S.enteritidis. This test is positive in 1st week of fever with a sensitivity of 86 % and specificity of 88 %. It will give negative result after the first week of the disease[39].

MOLECULAR METHODS

DNA probe: DNA probes specific to Vi antigen gene of S. typhi has been used for the diagnosis of organism from blood of patients with typhoid fever[13]. This can be done by concentrating the organisms either by lysis centrifugation system or by nylon filters to increase the sensitivity of the probe. The method is not as much of sensitive when compared to blood culture.

Polymerase chain reaction: PCR based test for detection of S.Typhi in the blood samples using flagellin gene has been tried. Two pairs of oligonucleotide primers, of which one is nested in the other, are used: Highly specific primers ST 1 and ST 2 are used in the first round of the PCR to amplify a 458 bp fragment. Nested PCR is highly specific. It can detect a bacterial load of 10^6 organisms. It is a useful test for early diagnosis of disease but test is not yet commercially available and difficult in areas where typhoid is endemic.

OTHER LABORATORY TESTS

Leukocytosis is seen in children and within the first 10 days of fever. Severe anaemia is unusual and may suggest complications. ESR is raised. Mild hyponatremia and Hypokalemia is common.

Diagnosis of Typhoid carriers

It is helpful to screen the food handling workers and cooks to identify carrier state. Carrier state can be determined by isolating the S. typhi in stool, bile or urine. The occurrence and amount of bacillary shedding varies and it is necessary, to test repetitive samples. For chronic carriers stool is preferred sample[38]. Diagnosis of urinary carriers requires repeated urine cultures.

Demonstration of Vi antigens is used as a screening test for carrier state. The test was found to be seventy percent sensitive. Other tests that can be used to distinguish carrier state were passive heamagglutination test, solid phase radioimmunoassay, CIE and ELISA. Carrier tracing in cities can be done by 'Sewer swab technique'.

DRUG RESISTANCE

CHLORAMPHENICOL AND TYPHOID

Chloramphenicol, was introduced for the therapy of typhoid fever around 1948 and was the 'gold standard' therapy since then.

MECHANISM OF ACTION

Chloramphenicol, was prepared from Streptomyces venezuelae in 1947. It is bacteriostatic but may be bactericidal in high concentrations. It has a wide spectrum of activity against gram-positive and gram-negative bacteria and binds to the 50S subunit of bacterial ribosomes, that inhibit peptide chain elongation[43].

RESISTANCE TO CHLORAMPHENICOL

Untill the 1972 it was the undoubted antibiotic for therapy of typhoid fever and lead to a decrease in mortality from 10% to < 2%. In 1950, Anderson et al first to report resistance to Chloramphenicol in S.Typhi isolates from England. The first epidemic of Chloramphenicol-resistant strain was observed in Mexico in 1972. Resistance to was encoded by a plasmid of the inc H 1 incompatibility group now termed incHI1 often in combination with resistance to streptomycin, sulfonamides, and Tetracyclines. (Rtype-CSSuT).

Resistance mechanisms to Chlormphenicol include enzyme inactivation by acetylation of the drug through Chloramphenicol acetyltransferases (CATs). These are encoded by the genes catA1,catA2, catB2 that have been demonstrated. Other mechanisms include

inactivation by phosphotransferases, efflux systems and mutation at target sites and loss of OMP.

MULTI DRUG RESISTANCE

With emergence of Chloramphenicol resistant S.Typhi and paratyphi A all over world, the focus shifted to other alternatives such as Ampicilllin, Co- trimoxable and Tetracycline. There was a good response to these drugs until resistace developed.

Multidrug resistance is defined as resistance to all the three first-line antibiotics -Ampicillin, Co-trimoxazole and Chloramphenicol[16].

MECHANISM OF ACTION

Trimethoprim inhibits the enzyme dihydrofolate reductase (DHFR) by binding to it's active site[44]. DHFR catalyses the reduction of DHFA to it's coenzyme tetrahydrofolate. Sulphonamide with it's structural analogy to paraminobenzoic acid inhibits the enzyme DHPS (dihydropteroate synthase) both of which are involved in folate synthesis required for thiamine production and bacterial growth.

AMPICILLIN

They inhibit bacterial replication by blocking the transpeptidation reaction of bacterial cell wall synthesis[44].

MECHANISMS OF RESISTANCE

Low level resistance to Trimethoprim is due to drug resistant variants of the chromosomal fol A gene encoding the bacterial DHFR. High level resistance is attained by bypass mechanism through genes that are plasmid mediated and consists of *dfrA1, dfrA3, dfrA10 and dfrB6.* Sulphonamide resistance is by mutations in the gene fol P that encodes for DHPS. Acquired resistance is by plasmid mediated genes such as sul 1 and sul2.

Resistance to Ampicillin is by production of β- lactamase enzymes that hydrolyze the β-lactam ring and sometimes by weakened penetration of drug to target PBPs (penicillin binding proteins) in the bacteria.

FLOUROQUINOLONES

The drug for MDR came with the discovery of Nalidixic acid, the prototype of the quinolones in 1962 during the purification of Chloroquine, a quinolone derivative.

MECHANISM OF ACTION

The main targets of flouroquinolones are bacterial enzymes DNA gyrase and DNA topoisomerse IV with 2 pairs of subunits. DNA gyrase is responsible for introducing negative super coiling in the DNA and for relieving topological stress during replication[44].

Quinolones attaches themselves to DNA gyrase or topoisomerase IV and induce a conformational alterations in the enzyme leading to the break the DNA and prevents relegation by producing a quinolone-DNA-enzyme complex.

MECHANISM OF RESISTANCE

Resistance to FQs is by two mechanisms, target mediated and non target mediated. Changesin the target enzymes, DNA gyrase and topoisomerseIV is the main mechanism of resistance. Other non target mechanisms include reduced accumulation either by efflux or by reduced uptake of drug, and plasmid mediated quinolone resistance[18].

Quinolone resistance in Salmonella is related with mutations in DNA gyrase mainly in the QRDR region of the A subunit. Plasmid mediated resistance genes of qnr (qnr A, qnr B, qnr S, and qnr D) and qnr S1 have been described.

NARST AND CIPROFLOXACIN

A few years after the introduction of fluoroquinolones , treatment failure was observed with ciprofloxacin. They were termed as NARST[18].

TREATMENT

TABLE 3 : TREATMENT OF TYPHOID FEVER[3]

	Optimal therapy			**Alternative effective drugs**		
Susceptibility	Antibiotic	Daily dose (mg/kg/day	Days	Antibiotic	Daily dose (mg/kg/day	Days
Uncomplicated Typhoid Fever						
Fully sensitive	Chloramphenicol	50-75	14-21	Fluoroquinolone, e.g. ofloxacin or ciprofloxacin	15	5-7
	Amoxycillin	75-100	14			
Multidrug-resistant	Flurosquinolone	15	5-7	Azithromycin	20	7
	or					
	Cefixime	15-20	7-14	Cefixime	15-20	7-14
Quinolone-resistant	Azithromycin	10-20	7	Cefixime		
	or					
	Ceftriaxone	75	10-17		20	7-14
Severe typhoid fever						
Fully sensitive	Ampicillin	100	14	Fluoroquinolone, e.g. ofloxacin or ciprofloxacin	15	10-14
	or					
	Ceftriaxone	60-75	10-14			
Multidrug-resistant	Fluoroquinolone	15	10-14	Ceftriaxone	60	10-14
				or		
				Cefotaxime	80	10-14
Quinolone-resistant	Ceftriaxone	60-75	10-14	Azithromycin	20	7
				Gatifloxacin	10	7

TREATMENT OF CARRIERS[41]

Carriers of S. Typhi should be decolonized to decrease the risk to close contacts . Carriers who have a normal gallbladder can be treated with high-dose intravenous ampicillin, oral ampicillin, or amoxicillin combined with probenecid for 6 weeks or, when a multiresistant organism is present, with a fluoroquinolone, such as norfloxacin or ciprofloxacin. Chronic carriers who cannot be decolonized are treated with cholecystectomy if cholelithiasis or cholecystitis is present; such patients should receive ampicillin intravenously 7 to 10 days before and 30 days after cholecystectomy.

TREATMENT OF RELAPSE[41]

The same therapy should be repeated with proper dose and duration after sending culture. In case, the empiric antibiotic is not sensitive then it should be changed to appropriate sensitive antibiotic and the total duration should be based on the antibiotic type.

PREVENTION

PUBLIC HEALTH MEASURES[40]

Recognition of an increased frequency of human infections with an unusual serotype should be followed by an epidemiologic investigation aimed at detecting the source and vehicle. Intervention to stop such

outbreaks then can be attempted. Careful food processing and storage, and proper preparation of foods are helpful in decreasing transmission of infection. Appropriate sewage disposal, assurance of a safe water supply and adequate cleaning of medical equipment are important public health strategies.

PERSONAL HYGIENIC MEASURES

Person-to-person spread can be decreased by hand washing after defecating or changing diapers, frequent hand washing during preparation of foods that might be contaminated (e.g .,meat), and excluding of infected individuals from food-handling tasks.

BREAST- FEEDING

In the developing world, breast-feeding is key in prevention because human milk contains secretory IgA and other factors that protects from S.Typhi.

VACCINATION[45]

Vaccines are available against typoid fever.

Whole cell inactivated typhoid/ paratyphoid vaccines (TA/TAB)

These were the initial vaccines available. They best suited for developing countries as they were effective in children, in expensive,

provide immunity for both typhoid and paratyphoid fever. Their enhanced reactogenicity led to discontinuation of use. They no longer available.

ORAL LIVE ATTENUATED TY21A VACCINE

This contains a live attenuated strain with a mutation of gal E gene and devoid of enzyme UDP gal 4 epimerase. It has genetical stability and not revert to virulence. It induces local gut immunity. It comes in enteric coated preparation as the organism is acid labile. It can be given to children 5 years of age and above as the capsules should be swallowed intact. 3 doses on alternate days in empty stomach is recommended. Antibiotics active against S.Typhi should not be used 3 days before and 3 days after intake of capsules. Immunity starts within a week after completing the course.

Vi CAPSULAR POLYSACCHARIDE VACCINE

This contains purified antigenic fraction of Vi capsular polysaccharide antigen of bacilli. Each dose having 25 microgram of purified polysaccharide in 0.5 ml of phenolic isotonic buffer for i.m or s.c use. This vaccine is not immunogenic below 2 years of age. The biological marker is anti Vi antibodies and 1 microgram per ml is taken as the serological correlate of immunity. This will not interfere with widal test results. It is recommended as a single dose in children aged 2 years

and above and can be given with all other vaccines. The dose should be repeated every three years.

Vi CONJUGATE TYPHOID VACCINES

Conjugation of the Vi antigen with a protein carrier would induce a T cell dependant immune response. Conjugation of Vi antigen with non toxic recombinant Pseudomonas aeruginosa exotoxin A has been evaluated in safety, immunogenicity and efficacy trials in Vietnam. Vi antigen conjugated with tetanus toxoid has been licensed recently in India. It can be given as two doses of 0.5 ml i.m at an interval of 4 to 8 weeks followed by a booster every ten years.

REVIEW OF LITERATURE

1. Gosai Mehul et al conducted a study at department of paediatrics, B.J Medical college, Ahmedabad during the year 2011. They included a 150 children with clinical and laboratory diagnosis of typhoid fever in their study and observed the variables such as age, sex, clinical features, laboratory results and antibiotic sensitivity vivo. Study shown male preponderance with male: female ratio of 1.38:1. Vomitting (86 %), abdominal pain (80 %) and loss of appetite (72%) are 3 frequent symptoms at the time of admission, next to fever. They found pallor (66 %), toxic look (98%), coated tongue (92%), hepatomegaly (53 %) and splenomegaly (22 %), icterus (8 %) in their study. The laboratory variables noticed are anemia (71 %), leucopenia (18 %), leucocytosis (2%), thrombocytopenia (3 %), elevated SGPT (10 %), positive Widal test (71%) and positive blood culture (5.33%). The mean defervescence period is 6.24 days. The antibiotic sensitivity pattern in vivo is resistance to ampicillin (78.12%), amoxycillin (77.5%), cotrimoxazole (84.2%), ciprofloxacin(19.5%) and cefotaxime (20%).

2. Nikhil patankar and Ira sha[15] carried out a study to evaluate age related clinical and laboratory manifestations of enteric fever in children. It was conducted during the year 2007 and at P J Wadia hostpital for children, parel, Mumbai. They included all the children with fever with

positive Widal test and/or positive blood culture. A retrospective analysis of clinical features laboratory parameters and antimicrobial therapy was done. A total of thirty three children were included and divided into two age groups; < 5year and > 5year. Mean age of presentation was 5±3 years. Male: Female ratio was 2:1. The observed variables were fever (100%), liver enlargement (82%), raised liver enzymes (85%), anemia (88%), elevated ESR (80%) and constipation (0%). In the < 5 year age group loose stools was common (p=0.05). Thirty percent patients not responded to 3rd generation cephalosporins as first line antibiotics. Complications noted in 18 % patients.

3. Ramaswamy ganesh et al[8] conducted a retrospective study at kanchi kamakodi CHILDS trust hospital, Nungambakkam, Chennai during the year 2010. 316 children were included in the study and 59% of them were not immunized with typhoid vaccine. They found eosinopenia (72%), increased incidence of Nalidixic Acid Recidence Salmonella Typhi (p<0.001) and elevated AST, eosinopenia, NARST as predictors of severity. The observed variables include vomiting (49%), loose stools (29%), liver enlargement (71%), splenomegaly (34%), mild elevation of liver enzymes (60%), moderate elevation in liver enzymes (14%) and normal liver enzymes (26%). The vaccine efficacy calculated is 32%, was calculated by using the formula (incidence among unimmunized – incidence among immunized)* 100/ incidence among unimmunized.

Complications noted in 4% of patients. They are SIRS (1.3%), hepatitis (0.63%), meningitis (0.3%), GI bleed (0.3%) and osteomyelitis(0.3%). The logistic regression analysis shown AST and spleen enlargement are considerably related to complicated enteric fever.

4. Jesudason MV and Sivakumar S[2] conducted a prospective study at Christian Medical College, Vellore during the year 2003. Blood samples for blood culture and typhidot test taken from 563 patients. Culture positivity noted in 39 patients. Study shown sensitivity (92.3%), specificity (98.8%), positive predictive value (85.7%) and negative predictive value (99.4%) for typhidot assay. Authors also concluded that Typhidot is a rapid, trustworthy and inexpensive investigation for typhoid fever and suitable for less equipped institutions.

5. Zohra begum et al[26]. and her colleagues done a study at mymensingh medical college, Bangladesh in the year 2006 to find out the reliability of Typhidot assay. They had taken 100 blood samples out of which 14 were positive blood culture method and 73 were positive in Typhidot (IgM) assay. The observations were the sensitivity (92.85%), specificity (90%), positive predictive value (76.47%), and negative predictive value (97.29%) for Typhidot assay. The study also included 20 febrile controls and 20 healthy normal controls. The Typhidot assay shown 20 percent false positive results in non typhoidal febrile group. But

false positive rate in healthy normal controls is 0%. This results indicates Typhidot assay may be a useful substitute for blood culture in endemic countries, where less facilities are available to do a blood culture. This is because of high sensitivity, specificity and negative predictive value of Typhidot assay.

6. During the year 2002, Jesudason M et al[2]. at Christian Medical College, Vellore conducted a study to estimate the efficacy of the Typhidot assay. Typhidot assay was done on 30 Widal positive sera, 30 sera from blood culture positive patients, 60 Widal negative sera and 30 sera from patients whom blood culture grew gram negative vacilli. The Typhidot assay had a sensitivity of 100% and specificity of 80% when bacteraemic patients were tested. The Typhidot assay was positive for both IgG and IgM in 39 sera, IgM alone in 24 sera and IgG alone in 2 sera.

7. Sonja J.Olsen et al[20]. evaluated 3 immunological rapid diagnostic methods namely multi test Dip-S-Ticks, Typhidot and TUBEX at two hospitals in Vietnam. The sensitivity and specificity finding were as follows; 89% and 53% for multi test Dip-S-Ticks , 79% and 89% for Typhidot 78% and 89% for TUBEX and 64% and76% for Widal test.

8. In a study of isolates from throughout the India during January 1990- August 1992. 65 percent of S. Typhi were found to be multidrug

resistant (MDR). The maximum number of MDR isolates was seen in central India (71%) whereas it was least in south (55%).

9. Between 1989-91, in a report by Jesudason MV et al[2], 11% of the S.Typhi isolates at Vellore Tamil Nadu were MDR. In another study by Padma Krishnan in Chennai, during 2007, 12% of S.Typhi isolates were found to be MDR out of a total of 50 isolates showing a significant decline.

10. An outbreak of typhoid due to multi-drug resistant S. Typhi was reported from Pondicherry, in south India by R. Sambasive Rao et al. the average prevalence of drug resistant strains in 1980-1988 had been 11.7%, which increased to 52% in 1989-1990. The majority of strains (80 %) were resistant to Choramphenicol, streptomycin, tetracycline and Ampicillin; 40% were resistant to Co-trimoxazole. Resistance was plasmid mediated and the strains belonged to Vi phage type O, biotype II. In 1996, Harish et al reported 33% MDR isolates of S.Typhi. Madhulika et al in 2003 reported 39 % of MDRST from Pondicherry.

AIMS AND OBJECTIVES OF THE STUDY

- To compare the reliability of typhidot assay and Widal test with gold standard blood culture method
- To study about clinical profile of typhoid fever in paediatric age group
- To study about antibiotic sensitivity pattern for enteric fever
- To study about response to treatment in enteric fever

STUDY JUSTIFICATION

* The emergence of multi drug resistance in S. Typhi to first line antibiotics such as ampicillin, chloramphenicol and cotrimoxazole has been a concern[18].

* The problem only worsened with the advent of NARST (Nalidixic acid resistant s.typhi) making ciprofloxacin a doubtful drug of choice for the treatment of enteric fever[18].

* With the changing patterns in antibiogram it is necessary to continually monitor the drug resistance pattern and understand the mechanisms involved, so that appropriate strategies can be adopted in the management of typhoid fever.

* During the 1st week of fever typhoid fever not easily differentiated from malaria, dengue fever, ricketsiosis and leptospirosis. The diagnosis of typhoid fever with gold standard blood culture method takes about minimum of 5-7 days.

* This study about the rapid serological diagnosis of typhoid fever by typhidot helps in ruling in or ruling out of the disease quickly so treatment of the typhoid fever can be initiated early without delay.

* It thus can help in preventing the morbidity, mortality associated with typhoid fever in children by initiating early intervention. There is regional difference in genomic structure and plasticity of the outer membrane protein of salmonella typhi, which is tested in typhidot assay.

Very few studies were done about typhidot assay in our part of country.

METHODOLOGY (MATERIALS AND METHODS)

* Study design – Prospective descriptive study

* Study place – Institute of Child Health and Hospital for Children, Egmore, Chennai

* Study period –April 2014 to November 2014

* Study population –children aged 3-12 years

INCLUSION AND EXCLUSION CRITERIA

- **Inclusion criteria**
    - Fever for ≥ 3 days without obvious focus of infection
    - Abdominal pain , constipation or diarrhoea
    - Coated tongue , toxic look
    - Hepatomegaly, splenomegaly
    - Relative bradycardia, rose spots
- **Exclusion criteria**
    - Children immunized with typhoid vaccine
    - Children suffering from fever other than typhoid
    - Children with documented typhoid fever within past 8 weeks

Sample Size

150

MANOEUVRE

* All children enrolled were subjected to detailed history and clinical examination. The following tests were done on the day of admission.

* CBC

* Peripheral smear

* Chest x ray

* Urine R/E and culture , sensitivity

* Liver function test

* Mantoux test

* Blood widal test

* Typhidot M assay

* Blood culture in brain heart infusion broth

* Empirical treatment with ceftriaxone will be started, if clinical improvement does not occur antibiotic will be changed according to antibiogram.

* Enrolled children were in follow up for defervesence of fever , complications, response to treatment ,hospital stay, alternative diagnoses if reached.

* At the end, descriptive analysis was done.

* Chi square test done for sensitivity, specificity, positive predictive value, negative predictive value for Widal test and Typhidot assay with comparing to gold standard blood culture method.

OBSERVATIONS & RESULTS

1. SEX DISTRIBUTION

A total of 167 children enrolled in the study. It includes 94 male and 73 female children.

TABLE 4

SEX			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Male	94	56.3
2	Female	73	43.7
3	Total	167	100

CHART 1

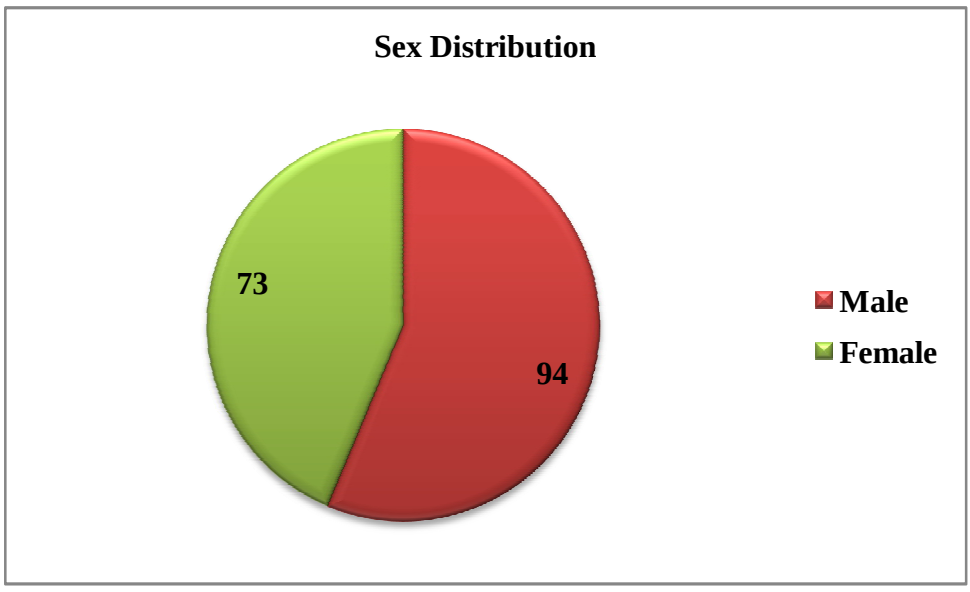
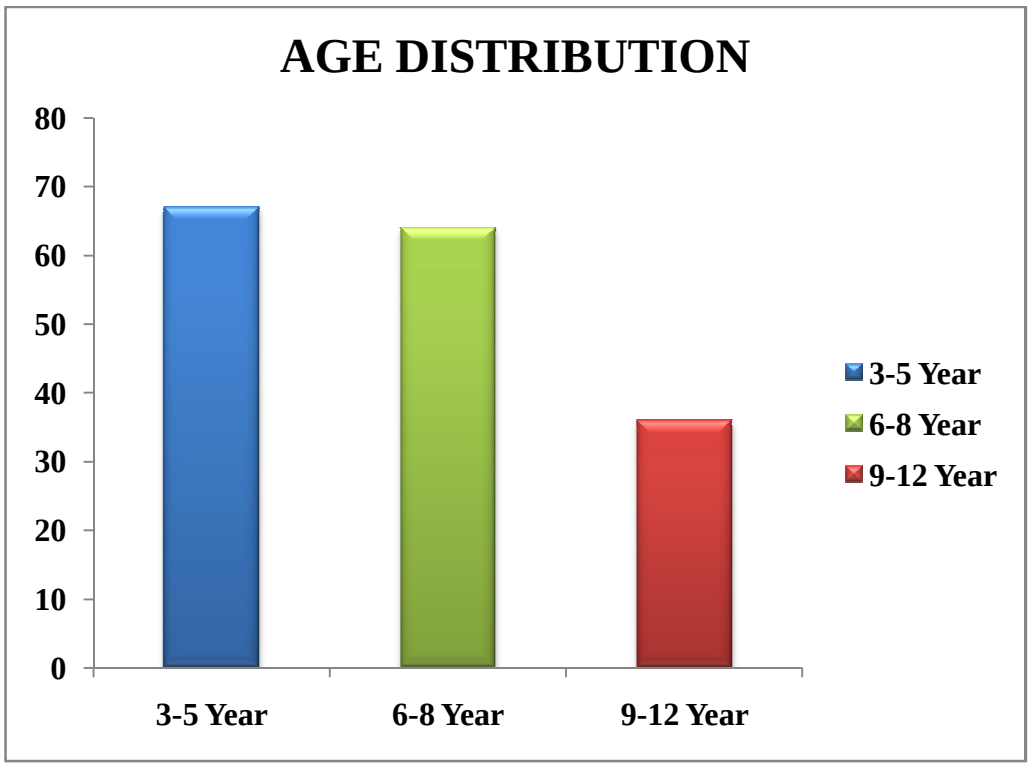


CHART 2



Out of 167 children 67 (40%) were in the 3-5year age group, 64 (38%) were in the 6-8 year age group, 36 (22%) were in the 9-12 year age group.

The whole study population can be divided in to three groups.They are non typhoidal illness, confirmed case of typhoid fever, probable case of typhoid fever.

CASE DEFINITION

NON TYPHOIDAL ILLNESS

115 (68.86%) children had other diagnoses like URI, Malaria, Acute viral fever, leptospirosis, Acute viral hepatitis and various other diagnoses and excluded from the study.

CONFIRMED CASE OF TYPHOID FEVER

Children with fever (38^0 C and above) for at least 3 days, and a positive blood culture. In this study 26 (15.56%) confirmed cases were present.

PROBABLE CASE OF TYPHOID FEVER

A children with fever (38^0 C and above) for atleast 3 days, with positive widal test result but negative result in blood culture method. In this study 52 (31.13%) probable cases were present.

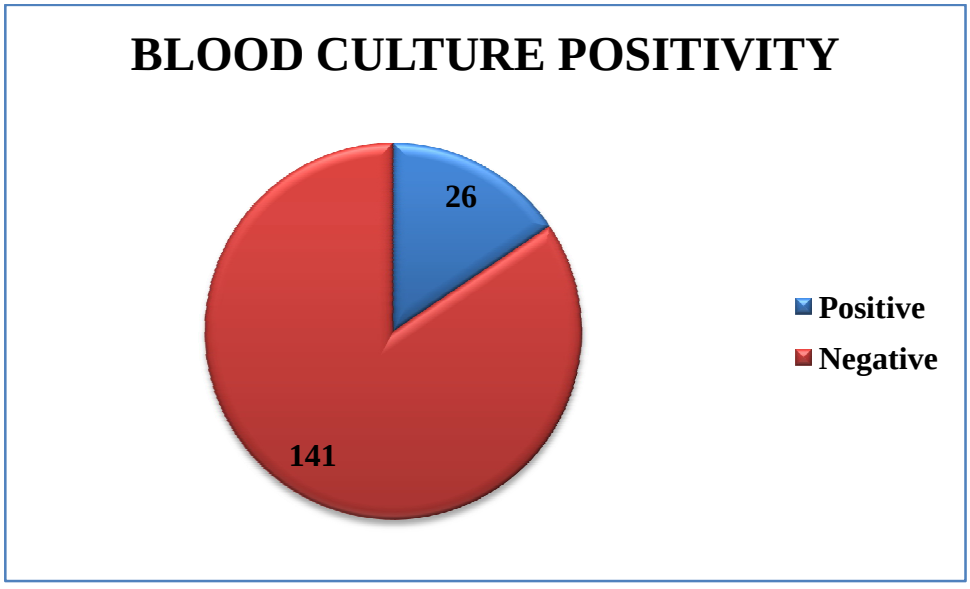
BLOOD CULTURE POSITIVE CASES

Out of 167 children, 26 (15.6%) children had S.Typhi grown in blood culture method.They are culture positive and confirmed cases of typhoid fever, since blood culture method is considered as gold standard method for diagnosing typhoid fever.

TABLE 5

BLOOD CULTURE POSITIVITY			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Positive	26	15.6
2	Negative	141	84.4
3	Total	167	100

CHART 3



Clinical features of this 15.6% patients will be described in following pages.

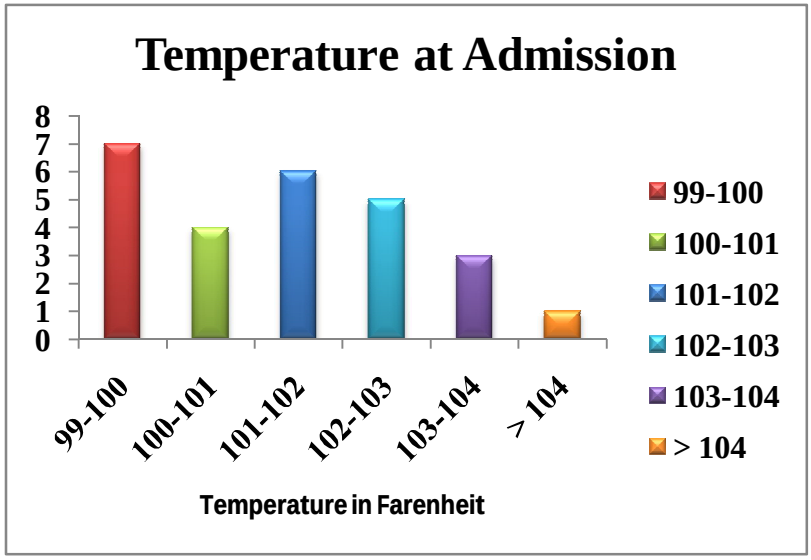
FEVER

All the 26 children had fever. Temperature profile at the time of admission is shown in the following table.

TABLE 6

TEMP. AT ADMISSION			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	99-100^0 F	7	26.9
2	100-101^0 F	4	15.4
3	101-102^0 F	6	23.1
4	102-103^0 F	5	19.2
5	103-104^0 F	3	11.5
6	> 104^0 F	1	3.8
7	TOTAL	26	100

CHART 4



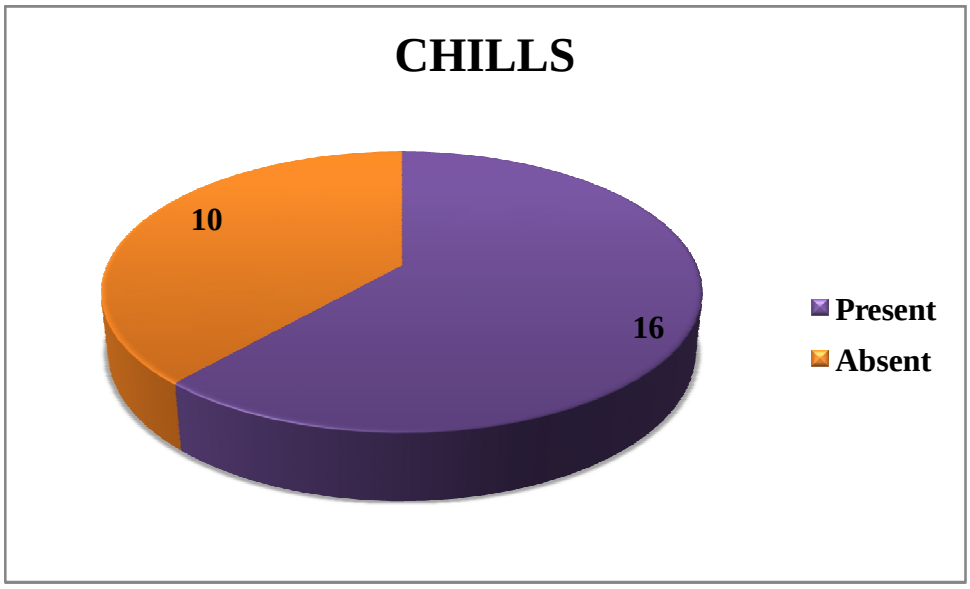
CHILLS

61.5% confirmed cases had chills.

TABLE 7

CHILLS			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	16	61.5
2	Absent	10	38.5
3	Total	26	100

CHART 5



CONSTIPATION

Out of 26, only one child had constipation (3.8%).

TABLE 8

CONSTIPATION			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	1	3.8
2	Absent	25	96.2
3	Total	26	100

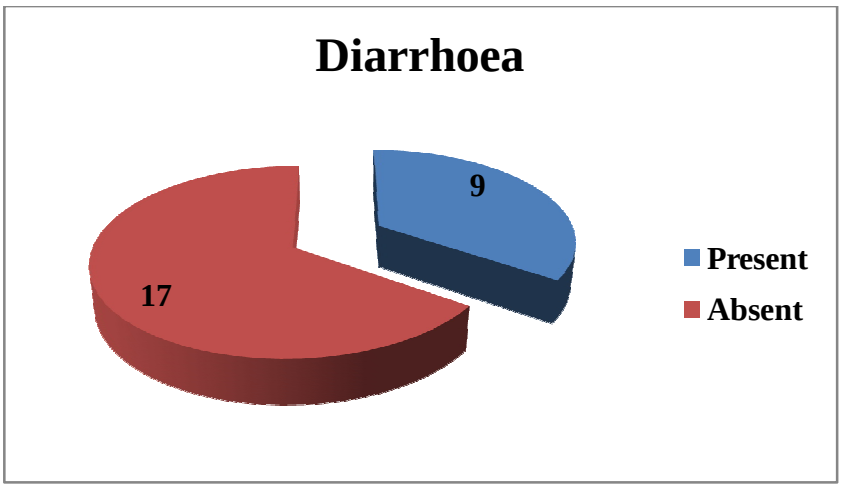
DIARRHOEA

Out of 26, only 9 children had diarrhoea (34.6%).

TABLE 9

DIARRHOEA			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	9	34.6
2	Absent	17	65.4
3	Total	26	100

CHART 6



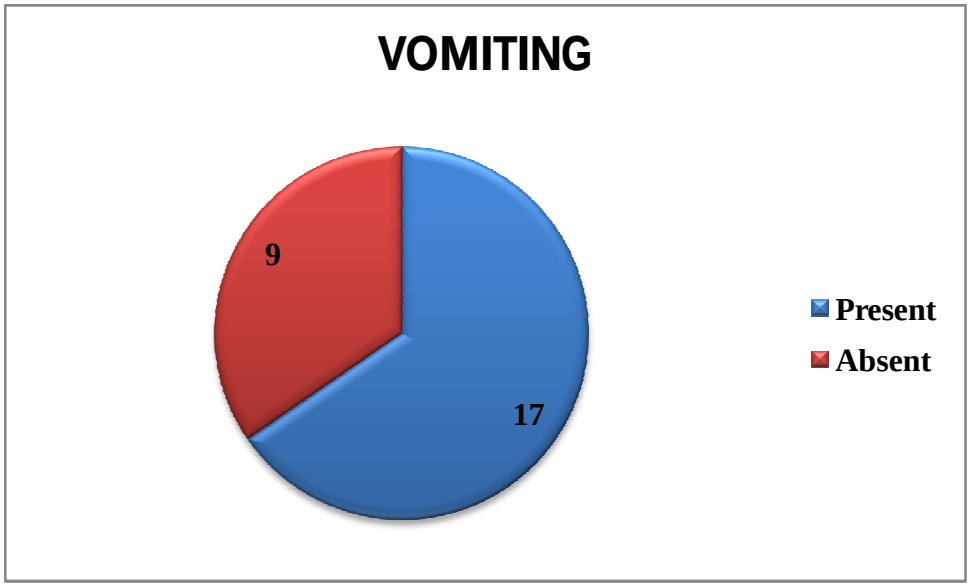
VOMITING

65.4% children had vomiting.

TABLE 10

VOMITING			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	17	65.4
2	Absent	9	34.6
3	Total	26	100

CHART 7



ABDOMINAL PAIN

12 children out of 26 had abdominal pain (46.2%).

TABLE 11

ABDOMINAL PAIN			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	12	46.2
2	Absent	14	53.8
3	Total	26	100

ABDOMINAL DISTENSION

Only 3 out of 26 had abdominal distension (11.5%).

TABLE 12

ABDOMINAL DISTENSION			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	3	11.5
2	Absent	23	88.5
3	Total	26	100

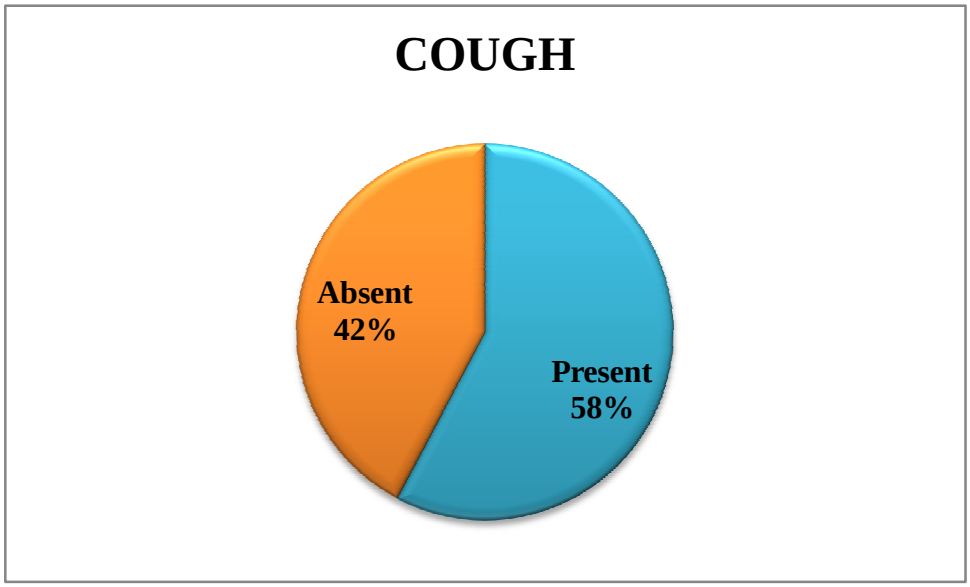
COUGH

57.7% patient had cough.

TABLE 13

COUGH			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	15	57.7
2	Absent	11	42.3
3	Total	26	100

CHART 8



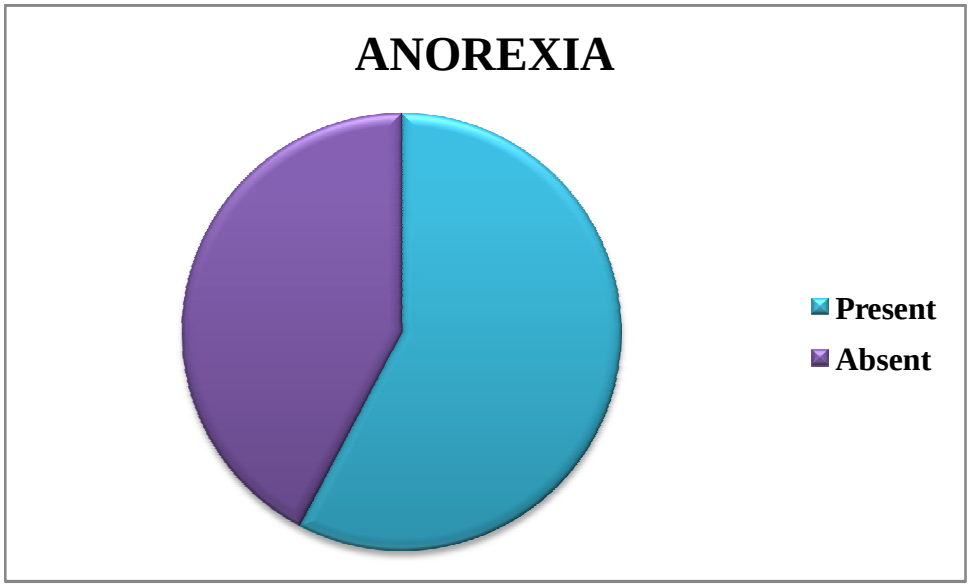
ANOREXIA

Out of 26, 17 patient had anorexia.

TABLE 14

ANOREXIA			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	15	57.7
2	Absent	11	42.3
3	Total	26	100

CHART 9



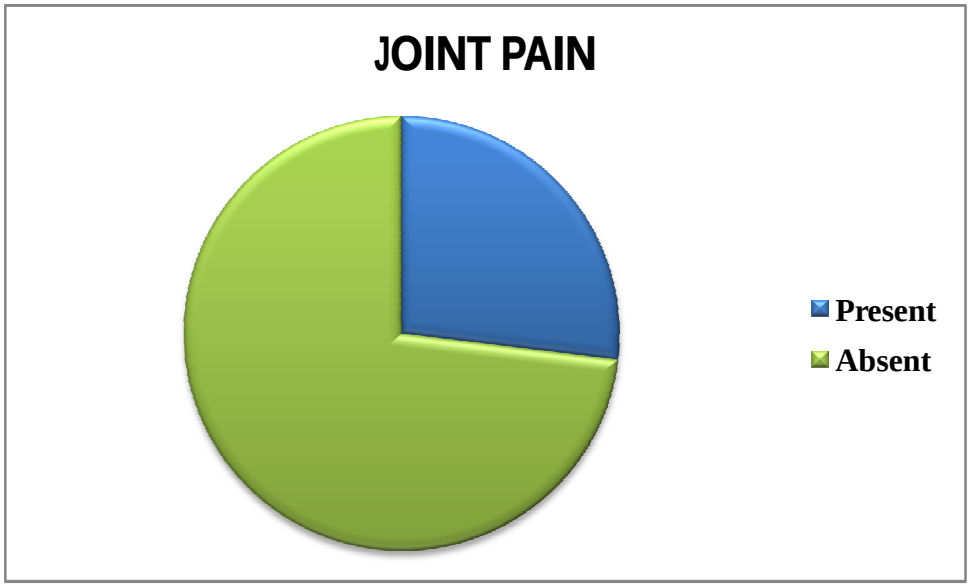
JOINTPAIN

Only 7 chidren out of 26 children, had joint pain.

TABLE 15

JOINTPAIN			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	7	26.9
2	Absent	19	73.1
3	Total	26	100

CHART 10



EPISTAXIS

Only one child had epistaxis (3.8%).

TABLE 16

EPISTAXIS			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	1	3.8
2	Absent	25	96.2
3	Total	26	100

HEADACHE

42.3% of patients had headache.

TABLE 17

HEADACHE			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	11	42.3
2	Absent	15	57.7
3	Total	26	100

ALTERED MENTAL STATUS

Only one child had altered mental status.

TABLE 18

ALTERED MENTAL STATUS			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	1	3.8
2	Absent	25	96.2
3	Total	26	100

SEIZURES AND LOSS OF CONSCIOUSNESS

None of the patient had seizures or loss of consciousness.

HISTORY OF CONTACT WITH TYPHOID FEVER PATIENT

One one child had history of contact with typhoid fever patient.

CLINICAL FEATURES

PALLOR

5 children out of 26 children had clinical pallor.

JAUNDICE

Non of the patient had clinically detectable icterus.

EDEMA

None of the child had edema.

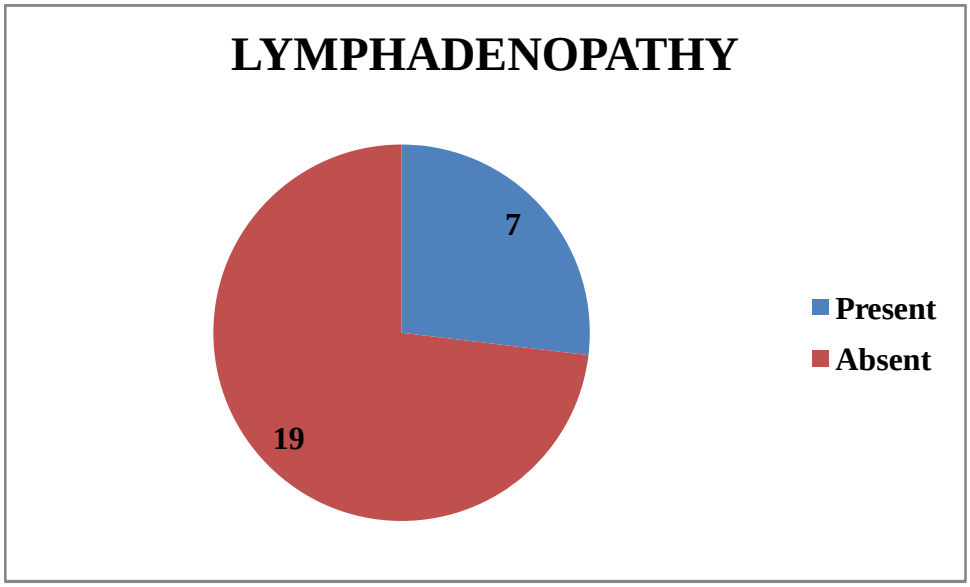
LYMPHADENOPATHY

26.9% children had lymphadenopathy.

TABLE 19

LYMPHADENOPATHY			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	7	26.9
2	Absent	19	73.1
3	Total	26	100

CHART 11



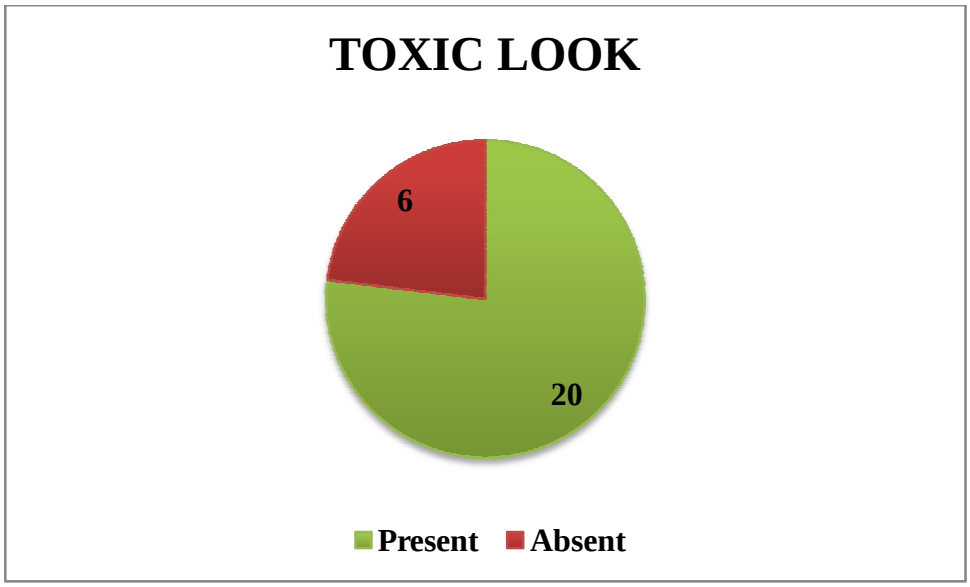
TOXIC LOOK

76.9% patients had toxic look.

TABLE 20

TOXIC LOOK			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	20	76.9
2	Absent	6	23.1
3	Total	26	100

CHART 12



ROSE SPOTS

None of the patients had rose spots.

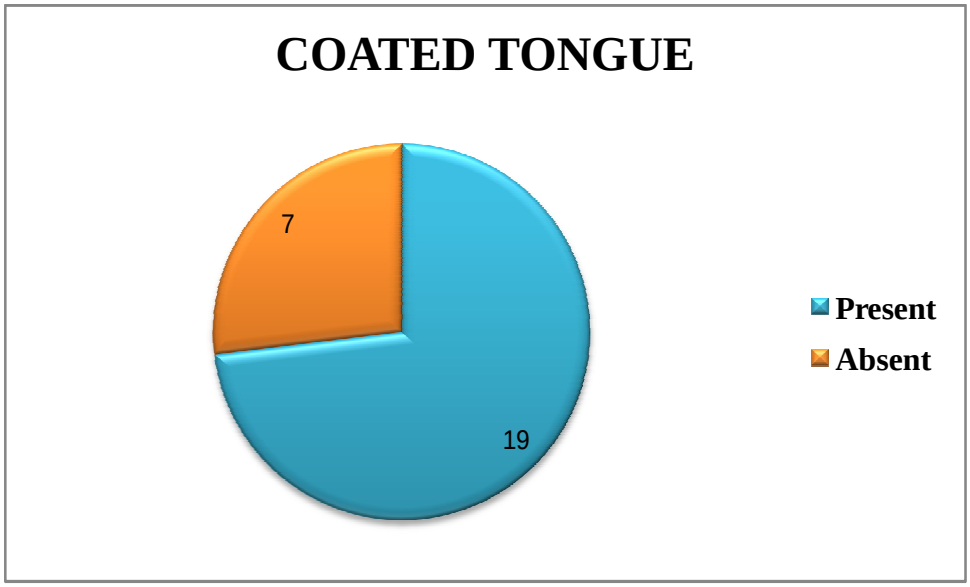
COATED TONGUE

Coated tongue noted in 73.1% of patients.

TABLE 21

COATED TONGUE			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	19	73.1
2	Absent	7	26.9
3	Total	26	100

CHART 13



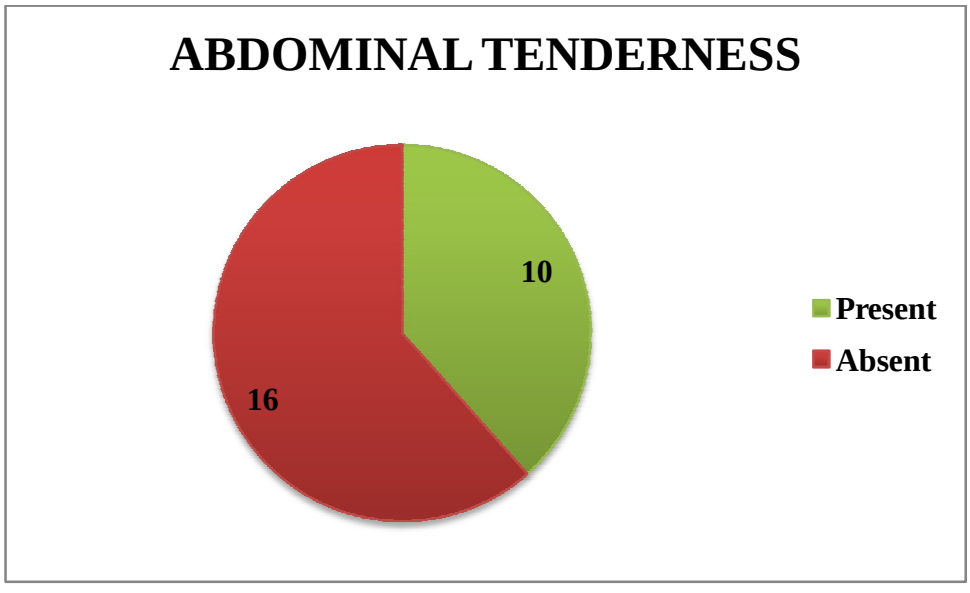
ABDOMINAL TENDERNESS

10 (38.5%) patients out of 26 patients had abdominal tenderness.

TABLE 22

ABDOMINAL TENDERNESS			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	10	38.5
2	Absent	16	61.5
3	Total	26	100

CHART 14



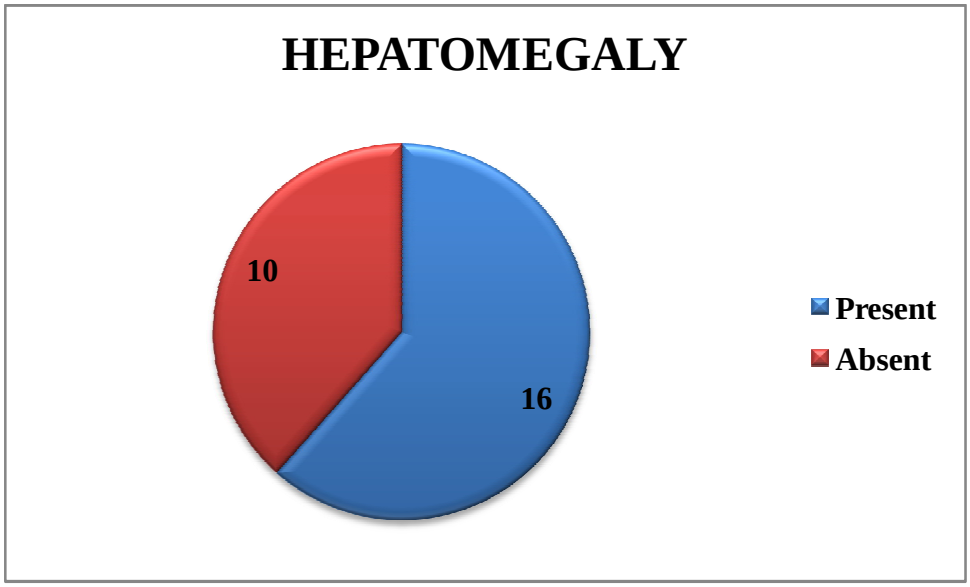
HEPATOMEGALY

Hepatomegaly is noted in 61.5% patients.

TABLE 23

HEPATOMEGALY			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	16	61.5
2	Absent	10	38.5
3	Total	26	100

CHART 15



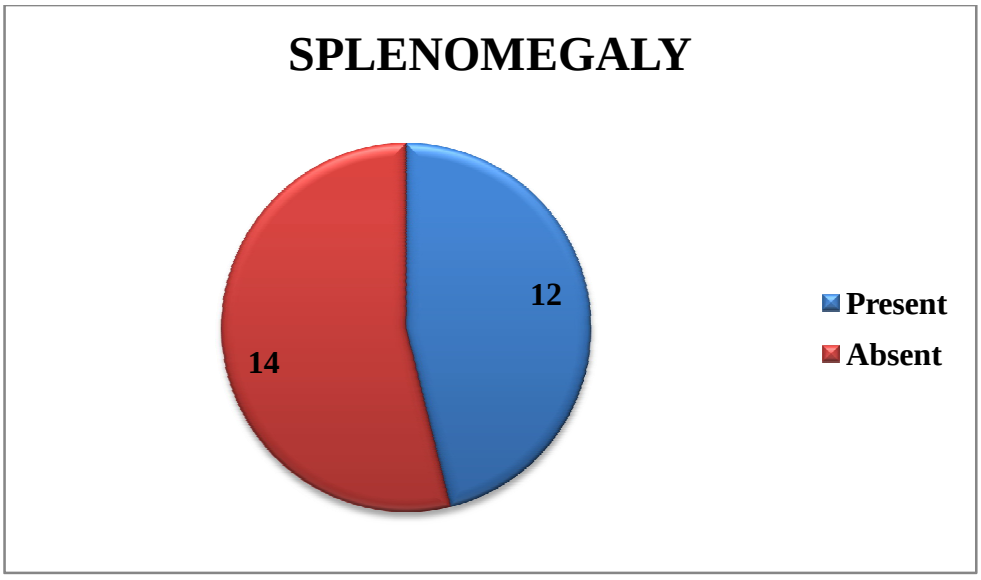
SPLENOMEGALY

12 (46.2%) patients out of 26 blood culture positive patients had splenomegaly.

TABLE 24

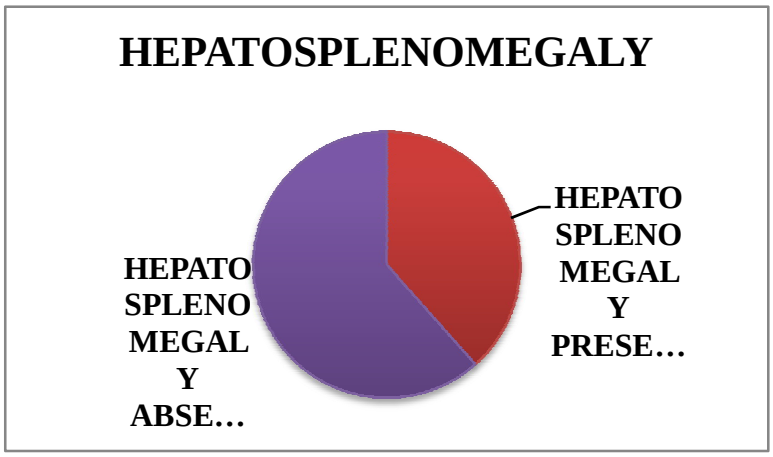
SPLENOMEGALY			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	12	46.2
2	Absent	14	53.8
3	Total	26	100

CHART 16



HEPATOSPLENOMEGALY

CHART 17



Out of 26 culture positive patients 38% (10) had both liver and spleen enlargement.

LUNG SIGNS

Lung signs (bronchial breath sounds, crackles, wheeze, tracheal deviation, etc.) are noted only in 2 (7.7%) patients.One child had wheeze, another had bilateral crepitations.

MURMER

Cardiac murmer noted in 2 patients (7.7%). but they were innocent murmers.

LABORATORY PARAMETERS

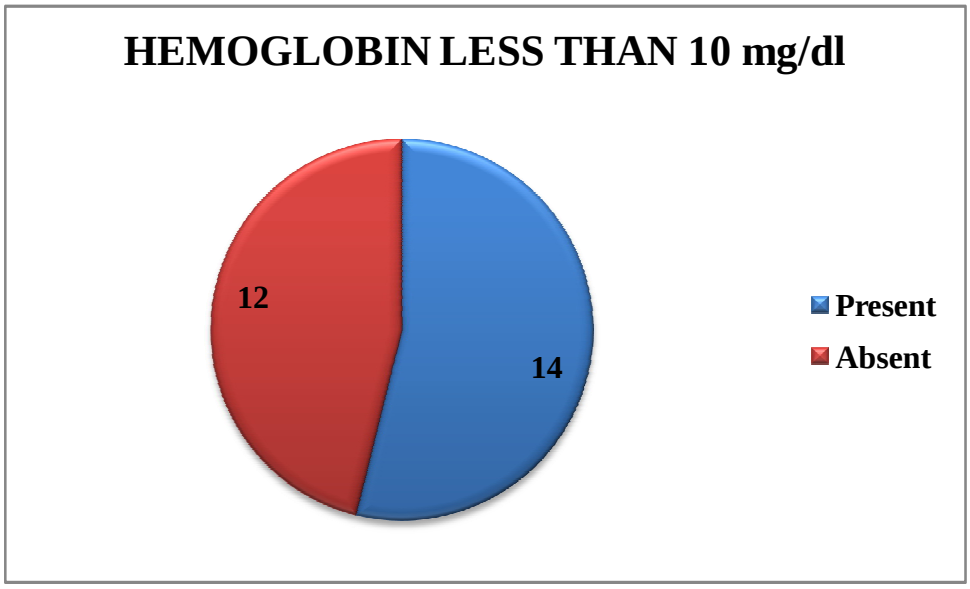
HEMOGLOBIN LESS THAN 10 mg/dl

53.8% patients had hemoglobin value less than 10 mg/dl.

TABLE 25

HEMOGLOBIN LESS THAN 10 mg/dl			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	14	53.8
2	Absent	12	46.2
3	Total	26	100

CHART 18



LEUCOPENIA

11.5% patients had leucopenia.

TABLE 26

LEUCOPENIA			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	3	11.5
2	Absent	23	88.5
3	Total	26	100

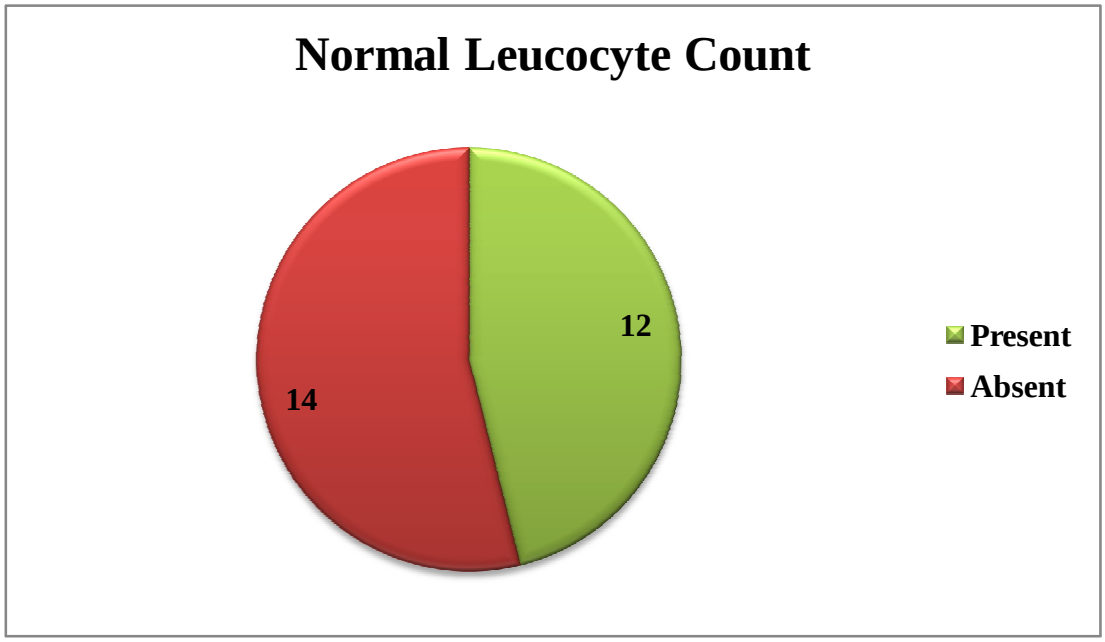
TOTAL WBC COUNT BETWEEN 4000 TO 10000.

This normal leucocyte count is noted in 46.2 % patients.

TABLE 27

TOTAL WBC COUNT BETWEEN 4000 TO 10000.			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	12	46.2
2	Absent	14	53.8
3	Total	26	100

CHART 19



LEUCOCYTOSIS

Total WBC count more than 10000 is noted in 42.3 % patients.

TABLE 28

LEUCOCYTOSIS			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	11	42.3
2	Absent	15	57.7
3	Total	26	100

THROMBOCYTOPENIA

Platelet count less than 100000 noted in only one patient.

TABLE 29

THROMBOCYTOPENIA			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Present	1	3.8
2	Absent	25	96.2
3	Total	26	100

URINE ALBUMIN AND URINE SUGAR

None of the patient in blood culture positive group showed urine albumin and urine sugar detection on urine routine examination.

URINE CULTURE AND SENSITIVITY

Only one patient had pathogenic bacterial growth in urine culture. He had associated urinary tract infection with E. coli.

PERIPHERAL SMEAR FOR MALARIAL PARASITE

None of the patient in blood culture positive for S.typhi group had malarial parasite in their peripheral smear.

CHEST X RAY

2 children out of 26 children had abnormal findings chest x ray. One had bilateral hyper ventilation, another one had pneumonitis patch in Right lower lobe.

SERUM BILIRUBIN LEVEL

None of the patient had elevated serum bilirubin level.

SERUM SGOT LEVEL

8 patients out of 26 had elevated serum SGOT level (30.8%).Out f this 8 patients 6 patients had mild elevation and 2 had moderate elevation in serum SGOT level.But none of the patient had marked elevation in serum SGOT level.

TABLE 30

SERUM SGOT LEVEL			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Elevated	8	30.8
2	Not elevated	18	69.2
3	Total	26	100

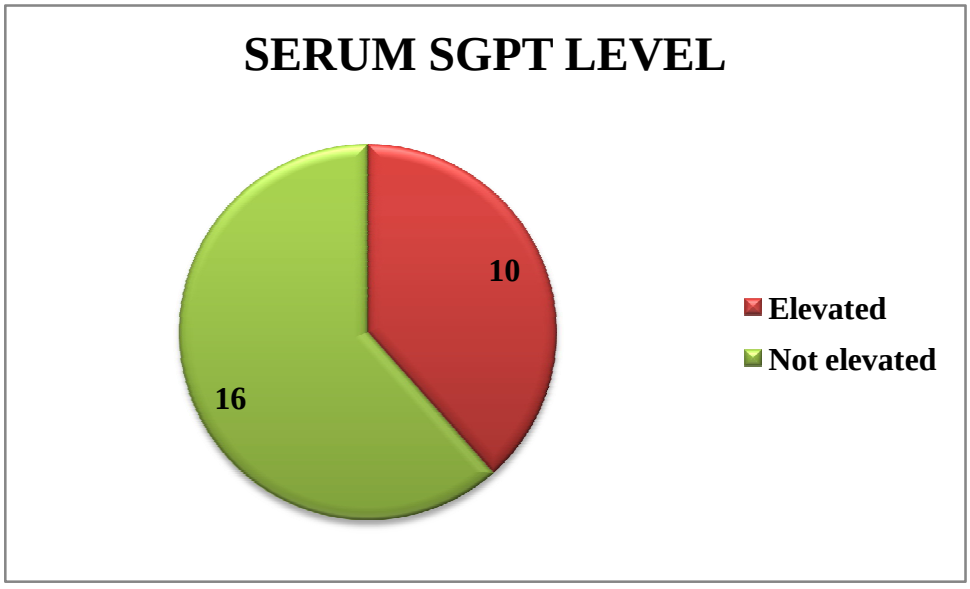
SERUM SGPT LEVEL

10 patients out of 26 (38.5%) patients had elevated serum SGPT levels. Out of this 10 patients, 7 patients had mild elevation and 3 patients had marked elevation.

TABLE 31

SERUM SGPT LEVEL			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Elevated	10	38.5
2	Not elevated	16	61.5
3	Total	26	100

CHART 20



MANTOUX TEST

None of the patient in 26 patients had positive Mantoux test.

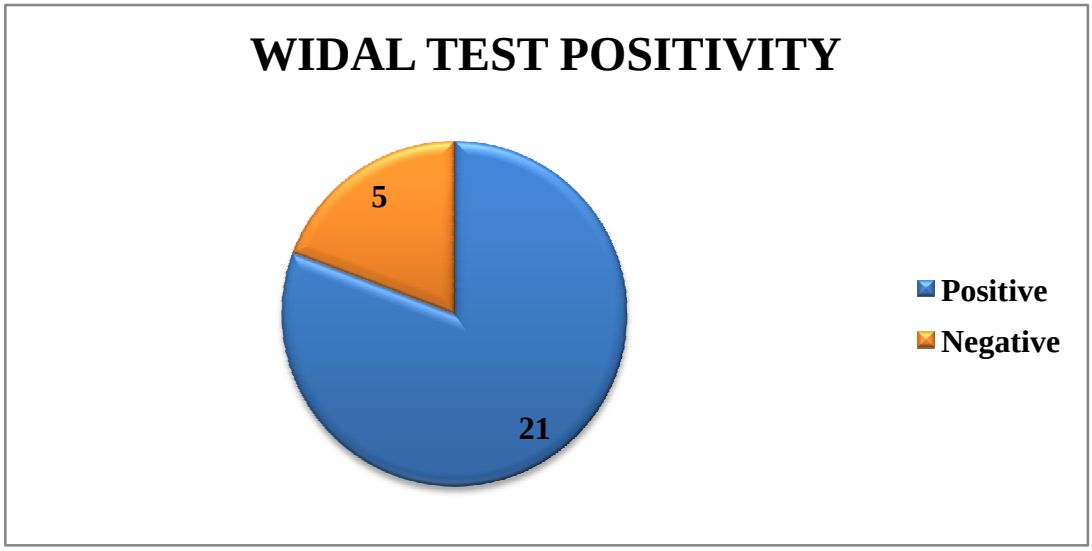
WIDAL TEST

21 patient out of 26 patients had positive widal test. This corresponds to 80.8% positivity in blood culture positive group.

TABLE 32

WIDAL TEST POSITIVITY			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Positive	21	80.8
2	Negative	5	19.2
3	Total	26	100

CHART 21



Titre O level is elevated upto 160 units in 13 patients

Titre O level is elevated upto 320 units in 8 patients.

Titre H level is elevated upto 160 units in 12 patients.

Titre H level is elevated upto 320 units in 8 patients.

TYPHIDOT ASSAY

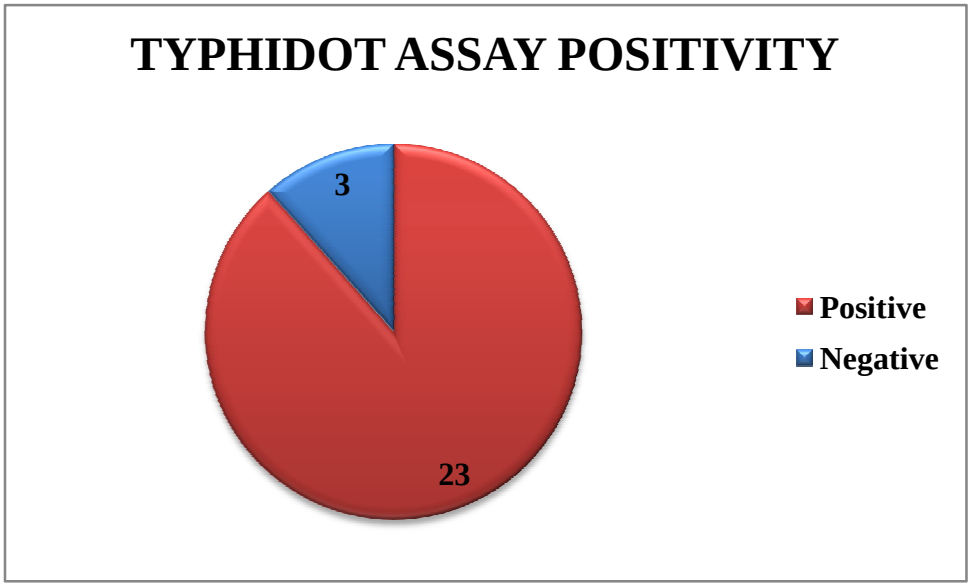
23 patients had positive typhidot assay, 3 patients had negative typhidot assay.

This corresponds to 88.5% positivity.

TABLE 33

TYPHIDOT ASSAY POSITIVITY			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	Positive	23	88.5
2	Negative	3	11.5
3	Total	26	100

CHART 22



ANTIBIOTIC SENSITIVITY PATTERN

AMPICILLIN

10 blood cultures (38.5%) were sensitive to ampicillin.

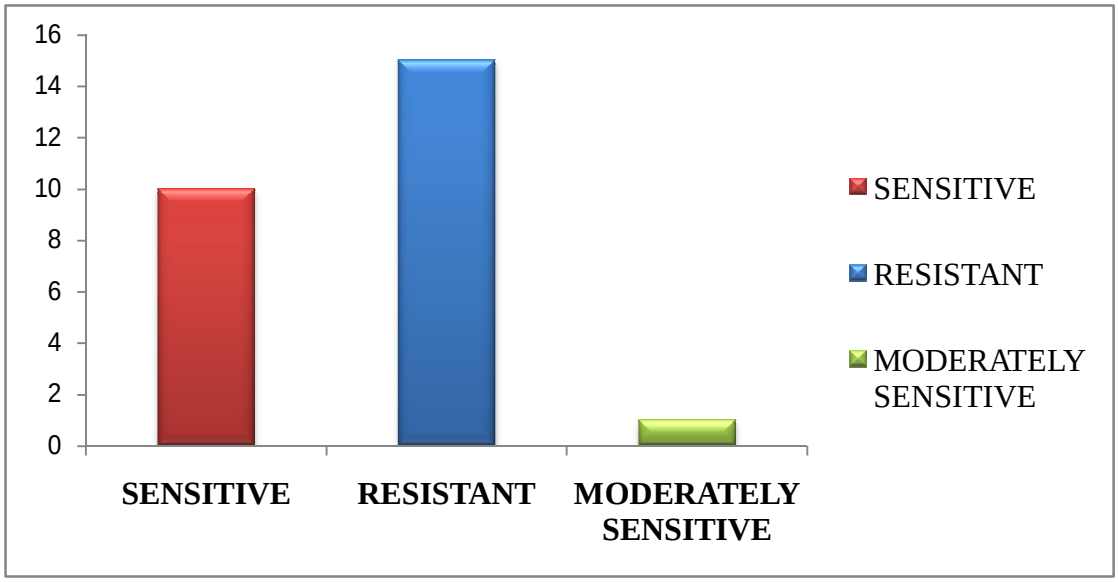
1 blood culture (3.8%) had moderate sensitivity.

15 blood cultures (57.7%) were not sensitive to ampicillin.

TABLE 34

AMPICILLIN			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	SENSITIVE	10	38.5
2	RESISTANT	15	57.7
3	MODERATELY SENSITIVE	1	3.8
4	Total	26	100.0

CHART 23



AMIKACIN

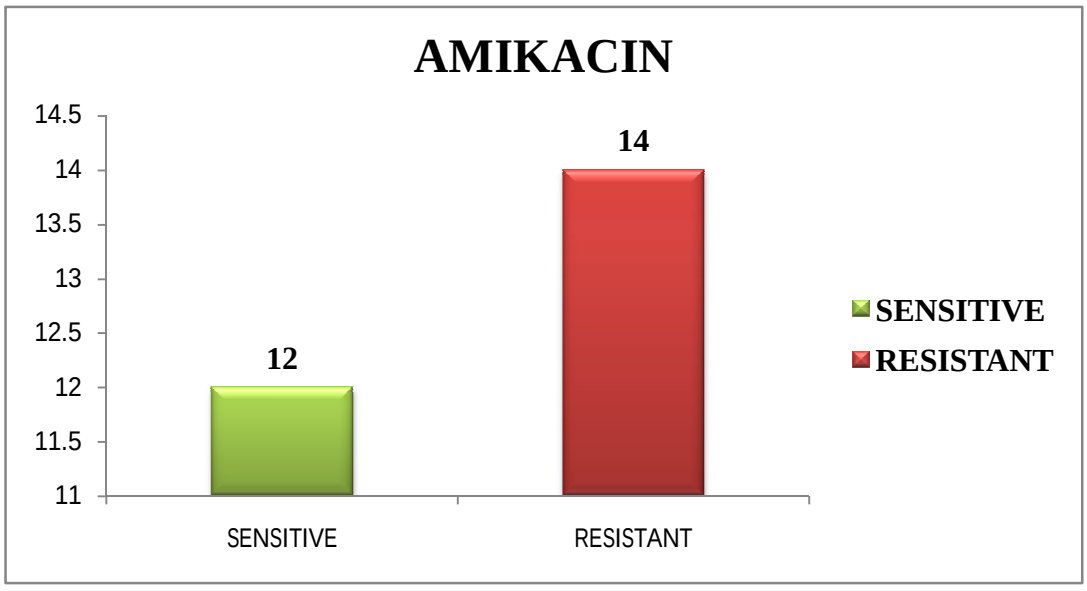
12 blood cultures (46.2%) were sensitive to amikacin sulphate.

14 blood cultures (53.8%) were resistant to amikacin sulphate.

TABLE 35

AMIKACIN			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	SENSITIVE	12	46.2
2	RESISTANT	14	53.8
3	Total	26	100.0

CHART 24



CIPROFLOXACIN

17 isolates (65.4%) were sensitive to ciprofloxacin.

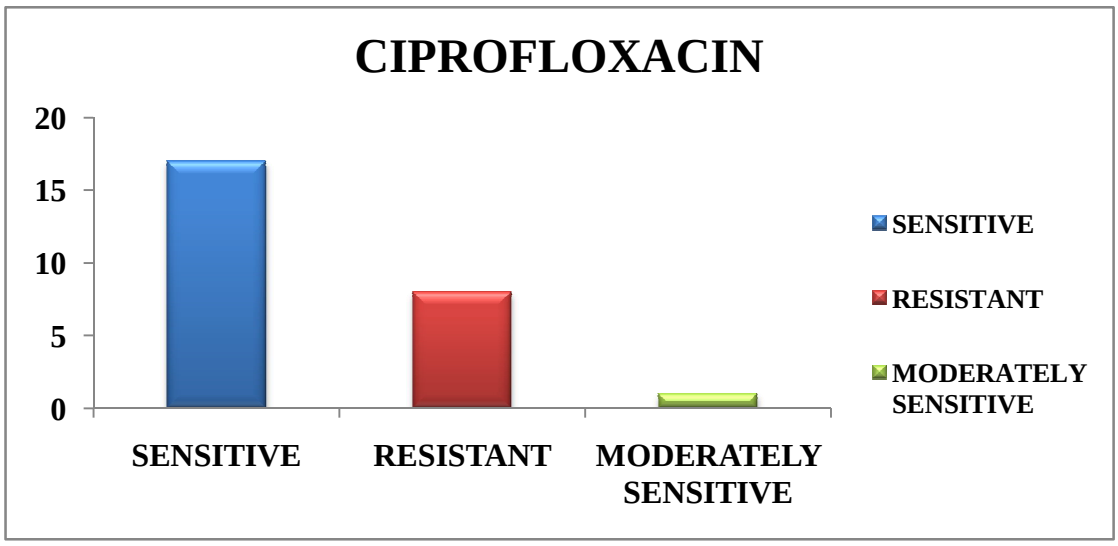
1 isolate (3.8%) had moderate sensitivity to ciprofloxacin.

8 isolates (30.8%) were not sensitive to ciprofloxacin.

TABLE 36

CIPROFLOXACIN			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	SENSITIVE	17	46.2
2	RESISTANT	8	53.8
3	MODERATELY SENSITIVE	1	3.8
4	Total	26	100.0

CHART 25



CEFOTAXIM

20 isolates (76.9%) were sensitive to cefotaxim.

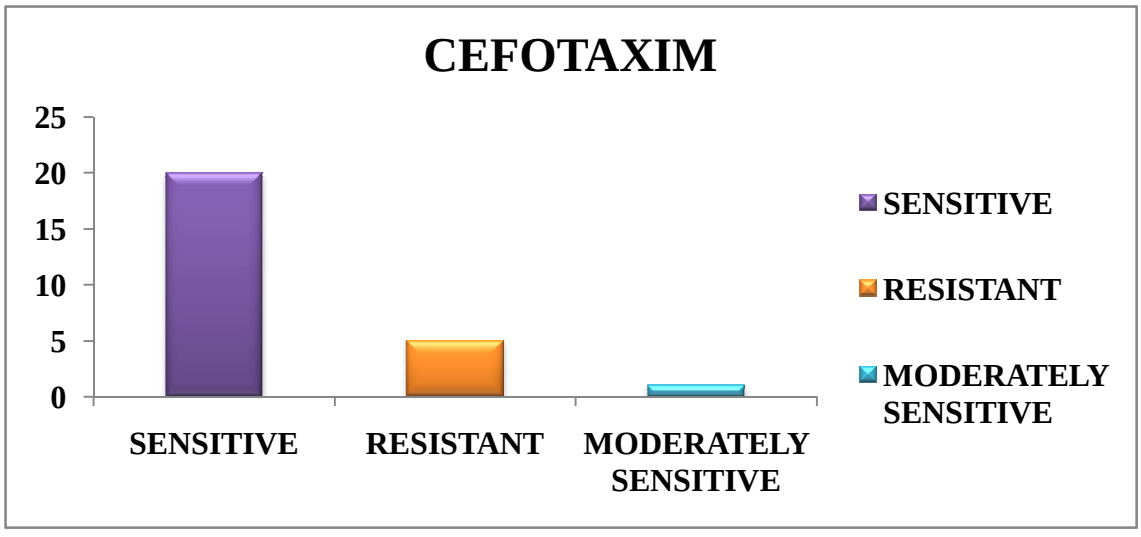
1 isolate (3.8%) had moderate sensitivity.

5 isolates (19.2%) were resistant to cefotaxim.

TABLE 37

CEFOTAXIM			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	SENSITIVE	20	76.9
2	RESISTANT	5	19.2
3	MODERATELY SENSITIVE	1	3.8
4	Total	26	100.0

CHART 26



CEFTRIAXONE

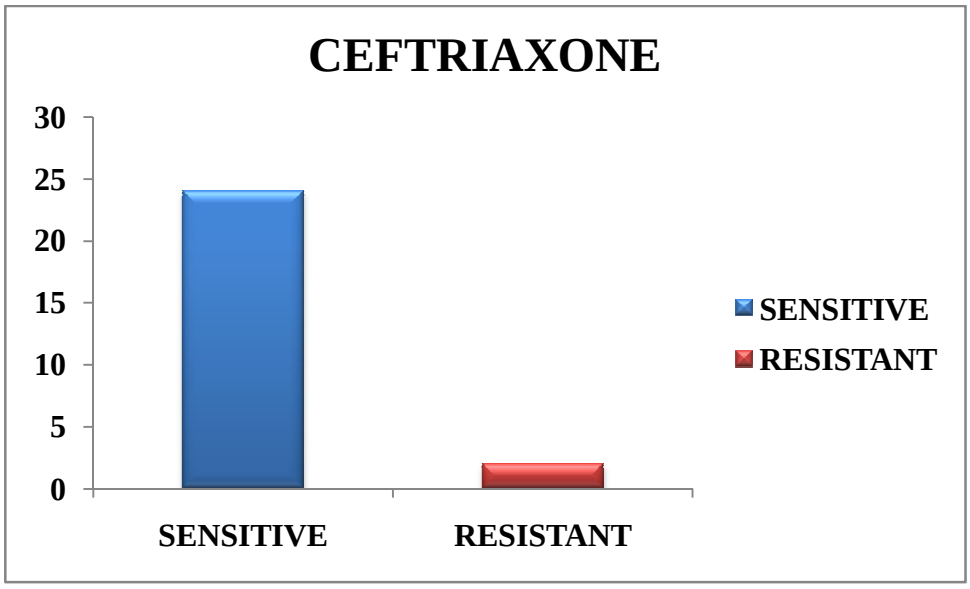
24 isolates (92.3%) out of 26 isolates were sensitive to ceftriaxone.

Only 2 isolates (7.7%) were resistant to ceftriaxone.

TABLE 38

CEFTRIAXONE			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	SENSITIVE	24	92.3
2	RESISTANT	2	7.7
	Total	26	100.0

CHART 27



CHLORAMPHENICOL

14 isolates (53.8%) were sensitive to chloramphenicol.

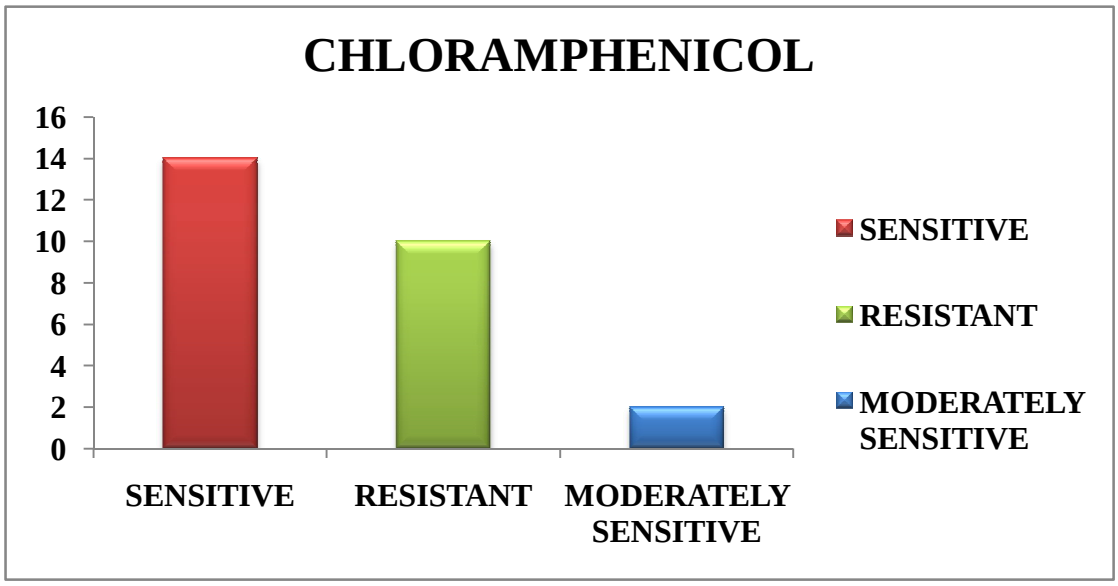
2 isolates (38.5%) were moderately sensitive to chloramphenicol.

10 isolates (38.5%) were resistant to chloramphenicol.

TABLE 39

CHLORAMPHENICOL			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	SENSITIVE	14	53.8
2	RESISTANT	10	38.5
3	MODERATELY SENSITIVE	2	7.7
4	Total	26	100.0

CHART 28



NALIDIXIC ACID

4 isolates (15.4%) were sensitive to nalidixic acid.

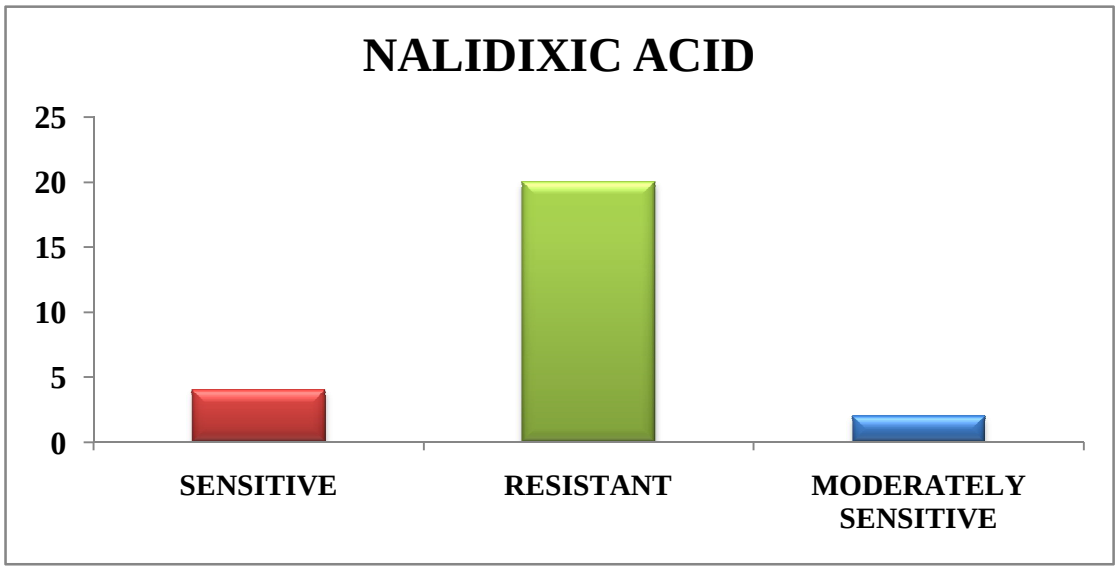
2 isolates (7.7%) were moderately sensitive to nalidixic acid.

20 isolates (76.9%) were resistant to nalidixic acid.

TABLE 40

NALIDIXIC ACID			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	SENSITIVE	4	15.4
2	RESISTANT	20	76.9
3	MODERATELY SENSITIVE	2	7.7
4	Total	26	100.0

CHART 29



COTRIMOXAZOLE

10 isolates (38.5%) were sensitive to cotrimoxazole.

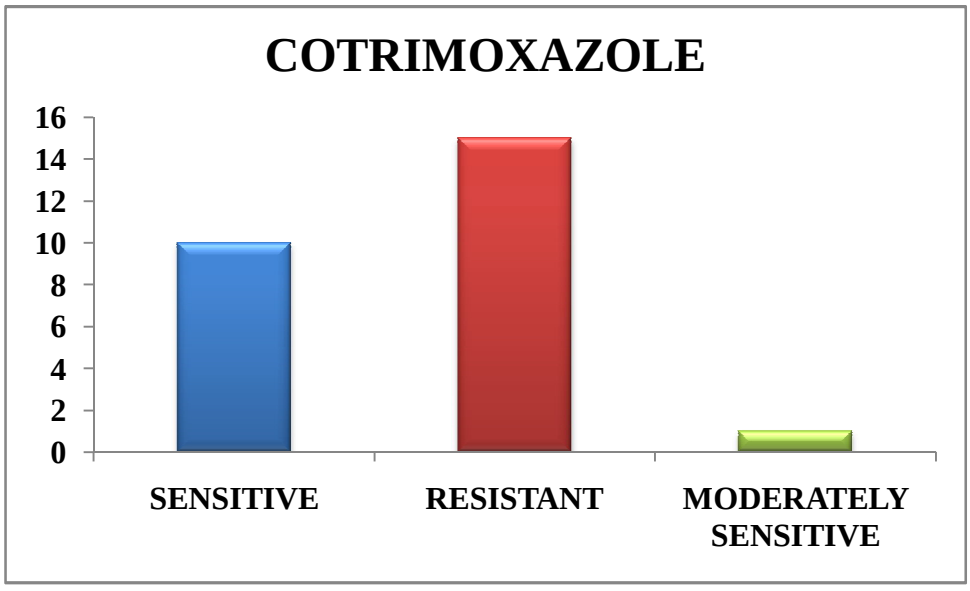
1 isolate (3.8%) had moderate sensitivity to cotrimoxazole.

15 isolates (57.7%) were resistant to cotrimoxazole.

TABLE 41

COTRIMOXAZOLE			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	SENSITIVE	10	38.5
2	RESISTANT	15	57.7
3	MODERATELY SENSITIVE	1	3.8
4	Total	26	100.0

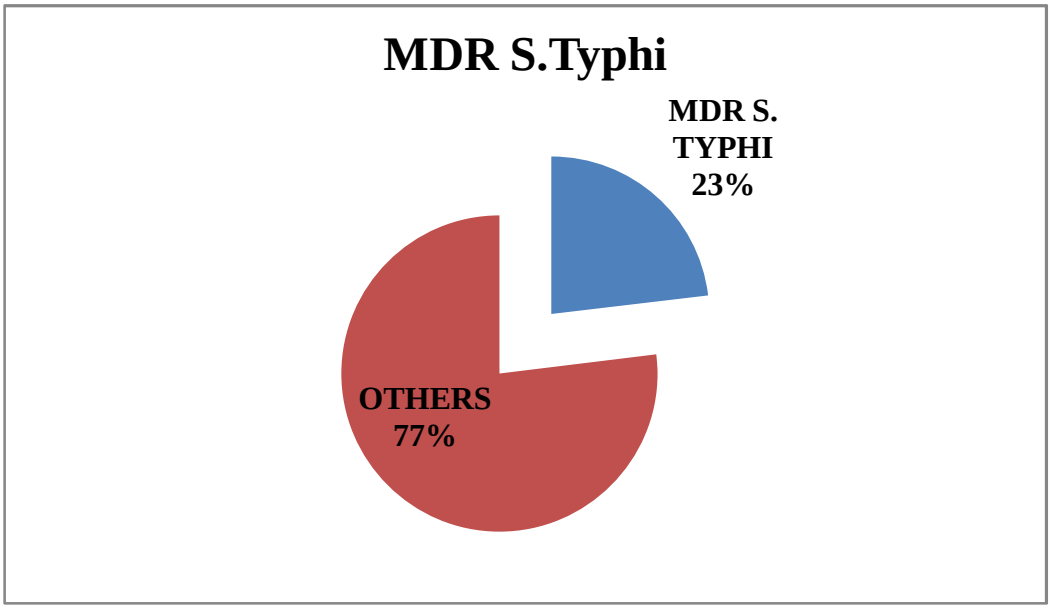
CHART 30



MULTIDRUG RESISTANCE

Isolates resistant to all the three firstline antibiotics viz . ampicillin, chloramphenicol, cotrimoxazole are MDR isolates. Incidence of MDR isolates in this study is 23%.

CHART 31



COURSE DURING THE HOSPITAL STAY

DAY ON WHICH FEVER DEFERVESCENCE OCCURS

Only one patient had fever defervescence on day 1.

Three patients had fever defervescence on day 2.

Four patients had fever defervescence on day 4.

Five patients had fever defervescence on day 5.

Five patients had fever defervescence on day 6.

Six patients had fever defervescence on day 7.

One patient had fever defervesence onday 8.

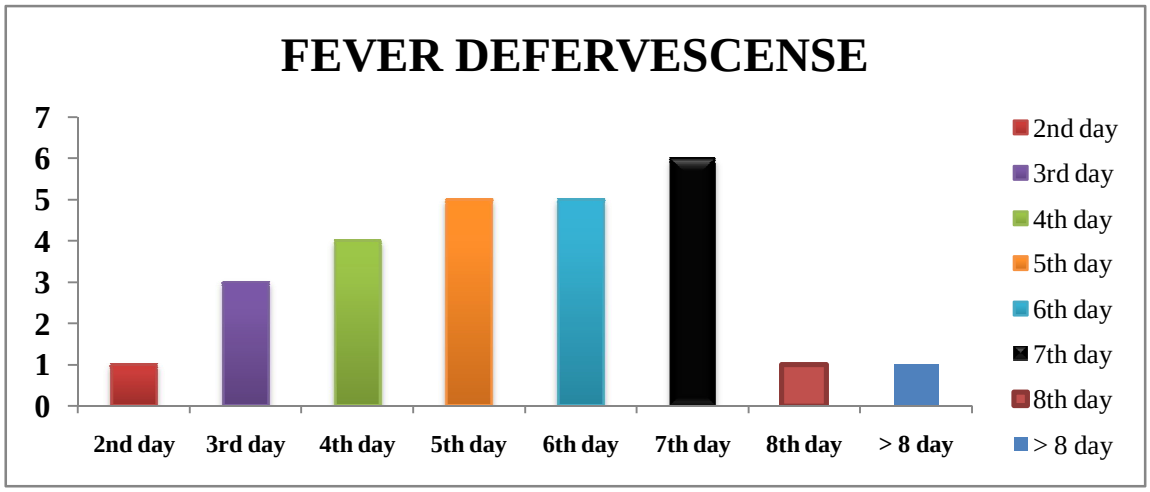
One patient had fever defervescence on day 12.

Mean value for fever defervescence is 5.28 days.

TABLE 42

FEVER DEFERVESCENSE			
Sl.No.	**Valid**	**Frequency**	**Percent**
1	2nd day	1	3.8
2	3rd day	3	11.5
3	4th day	4	15.4
4	5th day	5	19.2
5	6th day	5	19.2
6	7th day	6	23.1
8	8th day	1	3.8
9	> 8 day	1	3.8

CHART 32



CHANGES IN THE ORGANOMEGALY

This parameter is to note either increase or decrease in the size of organomegaly. Out of 26 patients only 6 had decrase in the size of hepatomegaly. No significant change is noted in 20 patients. No change is noted in the size of splenomegaly.

1 patient had decrease in hepatomegaly by 3rd day.

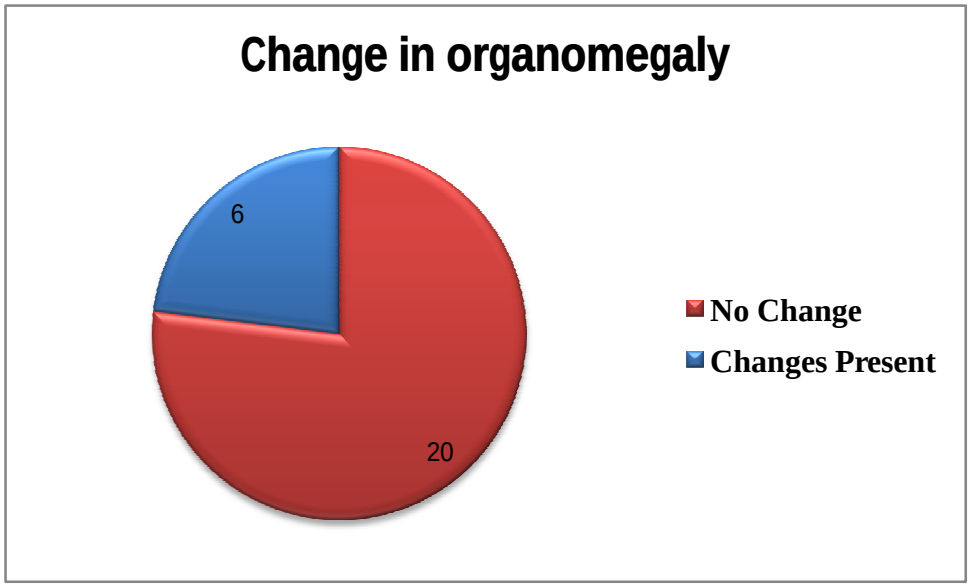
2 patient had decrease in hepatomegaly by4th day.

1 patient had decrease in hepatomegaly by 5th day.

1 patient had decrease in hepatomegaly by 6th day.

1 patient had decrease in hepatomegaly by 7th day.

CHART 33



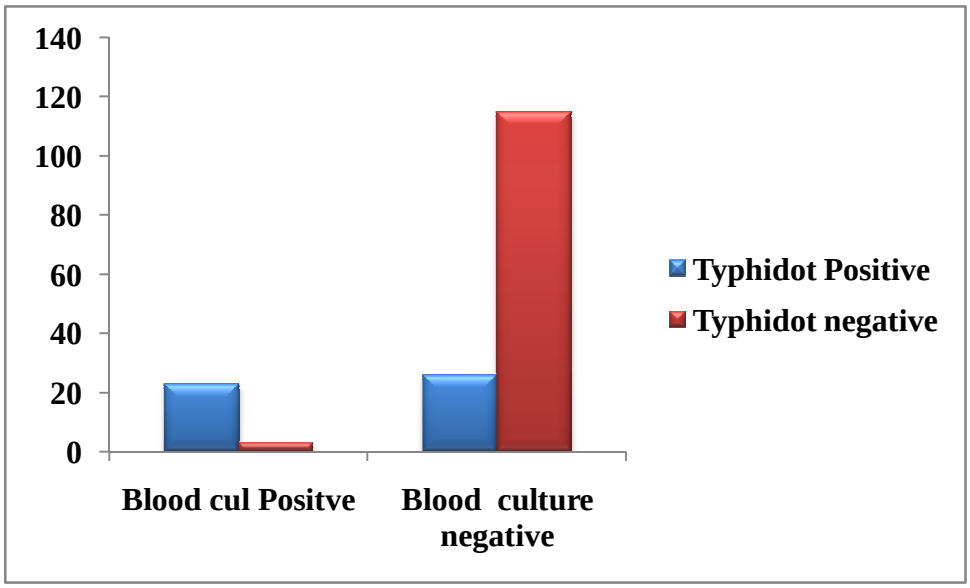
SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE, NEGATIVE PREDICTIVE VALUE OF TYPHIDOT ASSAY

Out of 26 blood culture positive cases which has taken as a gold standard was compared with the typhidot assay where 23 showed positive results and only 3 cases were negative by typhidot. The remaining 26 (out of 49) which were blood culture negative showed positive results with typhidot test. Typhidot assay had the sensitivity of 88.46%, specificity of 81.56%, positive predictive value of 46.94% and negative predictive value of 97.46% in comparison with blood culture results.

TABLE 43

CROSSTAB				
COMPARISON OF TYPHIDOT WITH BLOOD CULTURE				
		ENTERIC CULTURE		Total
		Positive	Negative	
TYPHIDOT	Positive	23	26	49
	Negative	3	115	118
Total		26	141	167

CHART 34



VALUES FOR TYPHIDOT ASSAY

TABLE 44

Chi-Square Tests for typhidot assay					
	Value	**df**	**Asymp. Sig. (2-sided)**	**Exact Sig. (2-sided)**	**Exact Sig. (1-sided)**
Pearson Chi-Square	51.916[a]	1	.000		
Continuity Correction[b]	48.593	1	.000		
Likelihood Ratio	48.738	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	51.605	1	.000		
N of Valid Cases	167				
a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 7.63.					
b. Computed only for a 2x2 table					

TABLE 45

Sensitivity	= **88.46 %**	95% CI: **69.82 %** to **97.42 %**
Specificity	= **81.56 %**	95% CI: **74.16 %** to **87.58 %**
Positive Likelihood Ratio	= **4.80**	95% CI: **3.30** to **6.97**
Negative Likelihood Ratio	= **0.14**	95% CI: **0.05** to **0.41**
Disease prevalence	= **15.57 %** (*)	95% CI: **10.43 %** to **21.97 %**
Positive Predictive Value	= **46.94 %** (*)	95% CI: **32.54 %** to **61.72 %**
Negative Predictive Value	= **97.46 %** (*)	95% CI: **92.74 %** to **99.44 %**

TABLE 46

Symmetric Measures					
		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.515	.074	7.205	.000
N of Valid Cases		167			
a. Not assuming the null hypothesis.					
b. Using the asymptotic standard error assuming the null hypothesis.					

SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE, NEGATIVE PREDICTIVE VALUE OF *WIDAL TEST* .

Out of 26 blood culture positive cases which has taken as gold standard was compared with the widal test where only 21 showed positive results and 5 were negative. The remaining 31 (out of 52) which were blood culture negative showed positive results with widal test. Widal test has sensitivity of 80.77%, specificity of 78.01%, positive predictive value of 40.38% and negative predictive value of 95.65% in comparison with blood culture results.

Cross tab for widal test

TABLE 47

		ENTERIC CULTURE		Total
		Positive	**Negative**	
WIDAL	**Positive**	21	31	52
	Negative	5	110	115
TOTAL		26	141	167

VALUES FOR WIDAL TEST

TABLE 48

Sensitivity	= 80.77 %	95% CI: 60.64 % to 93.37 %
Specificity	= 78.01 %	95% CI: 70.27 % to 84.54 %
Positive Likelihood Ratio	= 3.67	95% CI: 2.56 to 5.28
Negative Likelihood Ratio	= 0.25	95% CI: 0.11 to 0.54
Disease prevalence	= 15.57 % (*)	95% CI: 10.43 % to 21.97 %
Positive Predictive Value	= 40.38 % (*)	95% CI: 27.01 % to 54.90 %
Negative Predictive Value	= 95.65 % (*)	95% CI: 90.14 % to 98.56 %

TABLE 49

CHISQUARE TESTS FOR WIDAL TEST					
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	35.377[a]	1	.000		
Continuity Correction[b]	32.688	1	.000		
Likelihood Ratio	33.152	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	35.165	1	.000		
N of Valid Cases	167				
a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 8.10.					
b. Computed only for a 2x2 table					

TABLE 50

Symmetric Measures for widal test					
		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	**Kappa**	**.418**	.075	5.948	.000
N of Valid Cases		167			
a. Not assuming the null hypothesis.					
b. Using the asymptotic standard error assuming the null hypothesis.					

TYPHIDOT ASSAY POSITIVITY IN RELATION TO DURATION OF FEVER

CHART 35

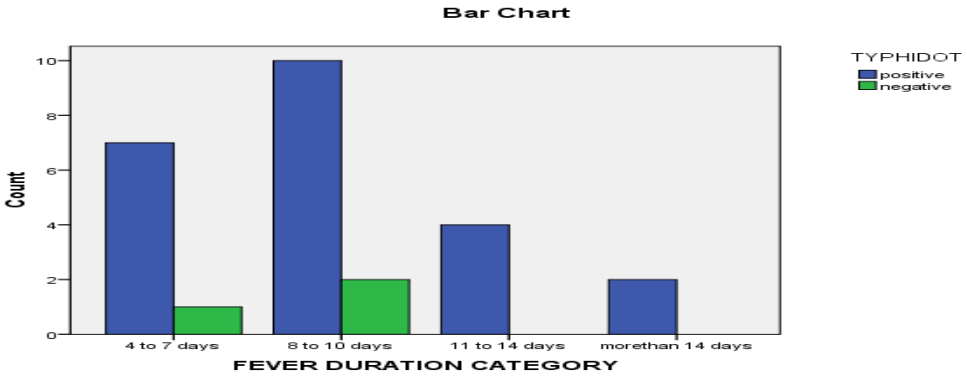


TABLE 51

NO OF DAYS OF FEVER * TYPHIDOT Crosstabulation				
Count				
		TYPHIDOT		Total
		positive	negative	
NO OF DAYS OF FEVER	4	2	9	11
	5	3	15	18
	6	5	14	19
	7	7	14	21
	8	6	9	15
	9	5	11	16
	10	4	18	22
	11	4	6	10
	12	3	3	6
	13	3	4	7
	14	2	4	6
	15	2	2	4
	16	1	1	2
	18	0	2	2
	20	2	3	5
	21	0	2	2
	30	0	1	1
Total		49	118	167

In this study 34.6% of positive results in typhidot assay obtained during first week of fever.

DISCUSSION AND SUMMARY

Though typhoid fever is a common infection in children, it is difficult to diagnose because of its nonspecific symptoms and signs. However it is necessary to diagnose early to initiate appropriate antibiotic therapy because delay in starting antibiotic treatment may lead to several morbidities and even death. The gold standard for diagnosing typhoid fever has always been the blood culture method. But the results of blood culture will be available only after a minimum of 5 days and need well equipped laboratory set up with experienced technical personals. It is costlier also. This delay may result in complications of typhoid fever.

Typhidot is one of the rapid diagnostic method available for diagnosis of typhoid fever. Its efficacy has been tested in various studies all around the world, but only very few studies have been done in our part of country. This study was primarily carried out to compare the typhidot assay with age old Widal test while taking blood culture as gold standard method and also to monitor the antibiotic sensitivity pattern and various clinical features of the typhoid fever.

AGE GROUP

The predominant age group in the study population was children 3-5 years old, accounting for (67) 40% of cases studied. The second common age group was children 6-8 years, about (64) 38%, followed by children aged 9-12 years about (36) 22%.

SEX

There was a total of 94 (56.3%) males and 73 (43.7%) females in study population. The male: female ratio in the study group was 1.28: 1, having male predominance.13 males (13.8%) and 13 females (17.8%) had a positive blood culture.

TYPHIDOT ASSAY

The sensitivity of typhidot assay is 88.56 % in this present study, which is comparable to most of the other studies.

Authour name/year	Sample size	Sensitivity (%)	Specificity (%)
K E Choo/1994	149	90%	91%
Butta ZA et al /1999	97	94%	89%
Jesudasan M et al /2002	150	100%	80%
Narayanappa et al /2010	105	92%	38%
Present study	167	88.46%	81.56%

So, typhidot fulfills one of the standard for an ideal diagnostic test as it does not usually miss the diagnosis when compared to blood culture. However three blood culture positive cases were had negative results in typhidot assay. These three false negative results may be due to covering of the Ig M antibody by Ig G antibodies during the second week of fever.

26 false positive results (out of 49) of typhidot observed. Interestingly 20 out of this 26 patients were also positive in widal test also. This finding could be attributed to

1. Endemicity of typhoid fever in the region signifying preexisting antibodies from earlier exposure or may be due to subclinical infection.

2. The patient may have had infection with non typhoidal salmonella serotype that share common antigens with S.Typhi.

Thus it can be considered that, though typhidot provided false positive results in 26 cases these patients may actually have had S. Typhi infection, either in the past or subclinical, which the blood culture failed to detect.

Analysis of the observations in this study, indicates that although blood culture is the gold standard for diagnosis of typhoid fever, typhidot assay might be a sensible alternative in the developing countries because of its high sensitivity, specificity and negative predictive value. Typhidot

will be particularly helpful in those areas where facilities for doing a blood culture is not available.

Furthermore manufacturer of typhidot says that it can become positive within 2-3 days of infection .In the present study 34.6% of positive results obtained during the first week of fever. Positive results seen from 4^{th} day onwards. But widal test will become positive only after the first week of fever, because antibodies to O and H antigens are produced only after first week. Thus, typhidot assay allows early recognition and treatment of typhoid fever.

Disadvantages of typhidot assay include

- It is costlier than widal test .
- It should be stored at 4-8^0 C. Cold storage is required for reagents.
- It does not give antibiogram.

WIDAL TEST

The sensitivity and specificity, negative predictive value of widal test in this study were 80.77%, 78.01%, 95.65% respectively. All of them lower than that of typhidot in this study. So it is less reliable than the typhidot test to diagnose typhoid fever in endemic regions. Further more it has the following disadvantages[23]

- It necessitates both acute and convalescent sera
- More time consuming
- Intrinsic inconsistencies with the test
- Difficulty in establishing a steady state baseline titre for the population.
- Recurrent exposures to S.typhi in endemic regions
- Cross reactivity with other non Salmonella organisms
- Lack of reproducibility of test results.

Despite all this limitations it is still in use particularly in areas that cannot meet the expense of the costlier diagnostic tests.

SYMPTOM ANALYSIS

The presenting symptoms of the 26 blood culture positive, confirmed cases of typhoid fever is as follows:

S.NO	SYMPTOM	FREQUENCY	PERCENTAGE
1	Fever	26	100%
2	Chills	16	61.5%
3	Constipation	1	3.8%
4	Diarrhoea	9	34.6%
5	Vomiting	17	65.4%
6	Abdominal pain	12	46.2%
7	Abdominal distension	3	11.5%
8	Cough	15	57.7%
9	Anorexia	17	65.4%
10	Joint pain	7	26.9%
11	Epistaxis	1	3.8%
12	Head ache	11	42.3%
13	Altered mental status	1	3.8%
14	Seizures	0	0.0%

From the above table we find the most commonest symptoms were fever with chills, vomiting, cough and anorexia which was present in more than half (50%) of the study population.

Fever is present in all of the patients. The mean value for duration of fever is 9.3 days.

CLINICAL SIGNS

The clinical signs observed in 26 culture positive confirmed cases is as follows;

S.NO	SIGNS	FREQUENCY	PERCENTAGE
1	Pallor	5	26%
2	Icterus	0	0%
3	Lymphadenopathy	7	26.9%
4	Toxic look	20	76.9%
5	Rose spots	0	0%
6	Coated tongue	19	73.1%
7	Abdominal tenderness	10	38.5%
8	Hepatomegaly	16	61.5%
9	Splenomegaly	12	46.2%
10	Hepatosplenomegaly	10	38.0%
11	Lung signs	2	7.7%

The most commonly observed clinical signs in this study are toxic look, coated tongue, hepatomegaly, splenomegaly. Incidence of hepatomegaly ranges from 30-70% in various studies. Incidence of splenomegaly ranges from 20-50% in various studies.

LABORATORY PARAMETERS

S.NO	LABORATORY PARAMETER	FREQUENCY	PERCENTAGE
1	ANEMIA	14	53.8%
2	LEUCOPENIA	3	11.5%
3	NORMAL LEUCOCYTE COUNT	12	46.2%
4	LEUCOCYTOSIS	11	42.3%
5	THROMBOCYTOPENIA	1	3.8%
6	URINE ALBUMIN	0	0.0%
7	URINE SUGAR	0	0.0%
8	URINE CULTURE	1	3.8%
9	SMEAR FOR MALARIAL PARASITE	0	0.0%
10	CHEST X RAY	2	7.7%
11	HYPERBILIRUBINEMIA	0	0.0%
12	SGOT ELEVATION	8	30.8%
13	SGPT ELEVATION	10	38.5%
14	MANTOUX TEST	0	0.0%

The most commonest laboratory parameters were anemia, normal WBC count and liver enzyme elevation. Reported incidence of anemia in typhoid fever varies from 30-60%, in various studies.

Most of the patients had normal leucocyte count in this study, which is similar to other studies.

Elevation of liver enzymes was observed in 38.5% patients, which is lower when compared to earlier study by Khosla et al which reported hepatic dysfunction in 55% of cases.

COMPARISON OF FEATURES IN BLOOD CULTURE POSITIVE AND TYPHIDOT POSITIVE GROUPS

S.NO	PARAMETERS	BLOOD CULTURE POSITIVE GROUP (%)	TYPHIDOT POSITIVE GROUP (%)
1	Cough	57.7%	42.9%
2	Vomiting	65.4%	69.4%
3	Abdominal pain	46.2%	53.1%
4	Diarrhoea	34.6%	36.7%
5	Abdominal distension	11.5%	12.2%
6	Anorxia	65.4%	59.2%
7	Altered mental status	3.8%	4.1%
8	Lymphadenopathy	26.9%	34.7%
9	Coated tongue	73.1%	69.4%
10	Toxic look	76.9%	67.3%
11	Abdominal tenderness	38.5%	51.0%
12	Hepatomegaly	61.5%	42.9%
13	Splenomegaly	46.2%	30.6%
14	Anemia	53.8%	49.0%
15	Leucopenia	11.5%	12.2%
16	Normal WBC count	46.2%	46.9%
17	Thrombocytopenia	3.8%	4.1%
18	Urine culture growth	3.8%	16.3%
19	Malarial parasite in PS	0.0%	8.2%
20	hyperbilirubinemia	0.0%	12.2%
21	Liver enzymes elevation	69.2%	73.5%

BLOOD CULTURE

Blood culture positivity in the present study is 15.6%, comparable to observations made in Kolkata (21%), bangladesh (14%) and several other studies. The comparatively lower sensitivity of blood culture was because of prevalent and ridiculous use of antimicrobial agents and also difficulties in drawing sufficient amout of blood for cultures in children.

ANTIBIOTIC SENSITIVITY PATTERN

S.NO	ANTIBIOTIC	SENSITIVE (%)	INTERMEDIATE (%)	RESISTANT (%)
1	Ampicillin	38.5%	3.8%	57.7%
2	Amikacin	46.2%	-	53.8%
3	Ciprofloxacin	65.4%	3.8	30.8%
4	Cefotaxim	76.9%	3.8%	19.2%
5	Ceftriaxone	92.3%	-	7.7%
6	Chloramphenicol	53.8%	7.7%	38.5%
7	Nalidixic acid	15.4%	7.7%	76.9%
8	Cotrimoxazole	38.5%	3.8%	57.7%

Ceftriaxone, cefotaxim and ciprofloxacin are three antibiotics having highest sensitivity in this study. This observation is similar those found in study of sherwal et al.

Incidence of Multi Drug Resistant S. Typhi in this study is 23%.Six out of 26 patients had MDR S.typhi. Four out of this six are under 5 years of age , 5 had both liver and spleen enlargement and one had splenomegaly only.

Incidence of Nalidixic Acid Resistant Salmonella Typhi is 76.9% and is higher than the resistance found in the study of Ramaswamy Ganesh et al. conducted during 2008, in this same Chennai. In his study he noted an increase in incidence of NARST from the year 2005 to 2008 (53% to 73%).Now, in this study it is almost 78%.

The antibiogram of S. typhi have been going through significant alterations over a period of time. Although multidrug resistance looks to be tapering at one end, there have been widespread reports of NAR in S. typhi and S. paratyphi all around the world that are responsible for decreased susceptibility to ciprofloxacin resulting in treatment failures and amplified chances of complications when flouroquinolones are used for management of typhoid fever.

RESPONSE TO TREATMENT

All the blood culture positive patients responded well to empirical ceftriaxone treatment and mean value for fever defervescence is 5.28 days.

46 out of 49 typhidot positive patients responded to empirical ceftriaxone and only three of them needed antibiotic change according to antibiogram.

CO-INFECTIONS

None of the culture positive patient had malarial parasite in their peripheral smear, even though coinfection with malarial parasite is common in tropical regions. But 3 patients (6.1%) in typhidot positive group had malarial parasite in peripheral smear.

Only one patient (3.8%) had culture proven urinary tract infection with E. coli. Positive mantoux test is not observed in any of the patients.

COMPLICATIONS

No mortality is noted in this study.

Intestinal hemorrhage, osteomyelitis, myocarditis, meningitis, infection associated hemophagocytic lymphohistiocytosis are not seen in any of the patient. 1 patient (3.8%) admitted with septic shock. 8 patient had evidence of typhoid hepatitis.

CONCLUSION

- Symptoms of the typhoid fever in children are non-specific, however presence of vomiting, abdominal pain, cough, anorexia and diarrhea in febrile child with history of fever more than 3 days should prompt the paediatrician to consider the possibility of typhoid fever. Likewise presence of toxic look, coated tongue, abdominal tenderness, hepatomegaly and splenomegaly in a febrile child are suggestive of typhoid fever.
- The laboratory parameters frequently associated with typhoid fever are anemia, normal WBC count and elevated liver enzymes.
- Typhidot assay is more sensitive, specific, rapid and has more predictability of a negative test when comparing to widal test. It can be used as a suitable alternative to widal test in regions where facilities for culturing the blood is not available to diagnose the typhoid fever.
- It is necessary to monitor the antibiotic sensitivity pattern as it is changing frequently over a period of time to avoid improper antibiotic usage, treatment failures and allowing the resistance to develop. The third generation cephalosporin Ceftriaxone is suitable for empirical first line therapy than Ciprofloxacin as there is a increasing trend in Nalidixic Acid Resistant Salmonella Typhi isolates.

LIMITATIONS OF THE STUDY

Sample size is smaller in this study. If more children were enrolled in the study a more detailed picture of clinical features and laboratory features could be obtained. Large scale prospective evaluation of typhidot assay in endemic popuations should be done to find the exact usefulness of typhidot assay.

FUTURE DIRECTIONS

Currently the blood culture is the gold standard investigation for diagnosing typhoid fever. But obtaining a positive culture is difficult because of widespread, rampant use of antibiotics before blood sampling and inherent variations of the blood culture to give positive result in relation to duration of fever. And also it is less sensitive than bone marrow culture which is a painful cumbersome procedure. To overcome this problem an alternative gold standard investigation should be established.

With the recent sequencing of the entire serotype Typhi genome, it may be possible to identify other antigens , such as fimbrial antigens that may produce an antibody response specific to serotype Typhi. Possibilities of more sophisticated molecular techniques for diagnosis like PCR, should be explored.

Proforma

CURRENT PATTERN OF ENTERIC FEVER IN CHILDREN:A PROSPECTIVE CLINICAL AND MICROBIOLOGICAL STUDY

Serial number: **Name:**

Age: **Sex:** **IP No:**

Address:

Date of admission:

Complaints:

Fever:

Duration:

Pattern:

Associated chills/rigor:

Bowel habits:(constipation/diarrhoea):

Vomiting:

Abdominal pain:

Abdominal distension:

Cough:

Anorexia:

Joint pain:

Myalgia:

Epistaxis:

Head ache:

Alteration in mental status:

Seizures:

Loss of consciousness:

H/o contact with known typhoid fever case:

Prior treatment history:

Immunisation for typhoid fever

Vital signs:

Pulse Rate:

Blood Pressure:

Respiratory Rate:

Temperature:

General examination:

Anemia:

Icterus:

Edema:

Lymphadenopathy:

Toxic look:

Rose spot:

Coated tongue:

Others:

Systemic examination:

Abdomen:

Respiratory system:

Cardio vascular system:

Central nervous system:

Musculo skeletal:

Investigations:

CBC

Urine R/E:

Culture & Sensitivity:

Peripheral Smear-MP:

Chest X Ray:

LFT: **Mantoux Test:**

Widal Test: **Titre: O H**

Typhidot Assay:

Blood culture:

Organism:

A\Ntibiotic Susceptibility Pattern

Ampicillin	Ciprofloxacin	Cotrimoxazole

Cefotaxim	Norfloxacin	Amikacin

Treatment:

Follow up:

Features	D1	D2	D3	D4	D5	D6	D7
Fever							
Organomegaly							
Complications							
Hospital stay							

Alternate diagnosis if reached:

ஒப்புதல்படிவம்

பெயர் தேதி

வயது பாலினம்

வரிசைஎண்

ஆய்விடம்: அரசினர்குழந்தைகள்நலமருத்துவமனை, எழும்பூர்சென்னை

ஆய்வாளர்:மரு.முகமதுரிபாயிஸ்அ. மு.

1. இந்தஆராய்ச்சியின்விவரங்களும்அதன்நோக்கங்களும்எனக்குமுழுமையாகவும்தெளிவாகவும்விளக்கப்பட்டது.
2. எனக்குவிளக்கபட்டவிவரங்களைநான்புரிந்துகொண்டுநான்எனதுகுழந்தையைஇந்தஆராய்ச்சிக்குஉட்படுத்தசம்மதிக்கிறேன்
3. இந்தஆராய்ச்சியின்தன்மைகளும்எனதுஉரிமைகளும்எடுத்துரைக்கப்பட்டது .
4. டைபாய்டுகாய்ச்சல்குழந்தைகளைஎவ்வாறெல்லாம்பாதிக்ககூடும்மற்றும்டைபிடாட்எனும்சோதனைஎந்தஅளவுக்குநம்பகதன்மையதுஎன்றும்சோதிக்கும்இந்தஆய்வில்எனதுகுழந்தைபங்குபெறசம்மதம்தெரிவிக்கிறேன்.
5. நான்எனதுகுழந்தையின்முந்தையமற்றும்தற்போதையமருத்துவவிவரங்களைஆய்வாளரிடம்தெரிவித்துவிட்டேன் .
6. இந்தஆய்வினால்ஏற்படவாய்ப்புள்ளஅபாயங்களைபற்றிஎனக்குதெரிவிக்கபட்டது

7. எனதுகுழந்தையின்உடல்நலம்பாதிக்கபட்டாலோஅல்லதுவழக்கத்திற்குமாறாகஅறிகுறிகள்தென்பட்டலோஉடனேஅதனைஆய்வாளரிடம்தெரிவிப்பேன்எனஉறுதிஅளிக்கிறேன்
8. நான்எனதுகுழந்தையைஇந்தஆய்வில்தன்னிச்சியாகஎந்தநிர்பந்தமும் இல்லாமல்பங்குபெறஅனுமதிக்கிறேன் .எந்தகாரணத்தாலும் , எந்தகாலகட்டத்திலும் ,எந்தசட்டசிக்கலும்இல்லாமல்நான்இந்தஆய்வில்இருந்துவிலகிகொள்ளலாம்என்றும்அறிந்துகொண்டேன்
9. நான்இந்தஆய்வின்மூலம்கிடைக்கும்தகவல்களையும்சோதனைமுடிவுகளையும்மற்றும்சிகிச்சைதொடர்பானதகவல்களையும்மருத்துவர் மேற்கொள்ளும்ஆய்வில்பயன்படுத்திகொள்ளவும்அதைபிரசுரிக்கவும் எனதுமுழுமனதுடன்சம்மதிக்கிறேன் .

பெற்றோர்/பாதுகாவலரின்

கையொப்பம்மற்றும்பெயர்

ஆய்வாளர்கையொப்பம்

(மரு.முகமதுரிபாயிஸ்அ. மு.)

தேதி

இடம்

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MASTER CHART

NAME	AGE	SEX	DURATION OF FEVER	DIARHOEA	VOMITING	ABDOMINAL PAIN	COUGH	ANOREXIA	LYMPHADENOPATHY	TOXIC LOOK	COATED TONGUE	HEPATOMEGALY	SPEENOMEGALY	Hb LESS THAN 10	TC 4000-10000	URINE CULTURE	SMEAR FOR MP
kural alagan	10	1	11	1	1	1	2	1	2	1	1	1	2	1	1	2	2
mariyammal	8	2	5	1	1	2	1	1	2	2	2	2	2	2	1	1	2
tejasri	6	2	10	2	1	2	1	2	1	2	1	1	1	1	2	2	2
manimaran	7	1	4	1	1	1	1	1	2	1	1	1	1	2	1	2	2
priya	5	2	9	1	2	2	2	2	2	2	2	1	2	2	2	2	2
varsini	4	2	6	2	1	2	1	2	1	1	1	2	2	2	1	2	2
saisaranya	5	2	7	1	1	2	1	1	2	1	1	1	1	2	1	2	2
sabarivasan	7	1	9	1	1	2	1	1	2	1	1	2	2	1	2	2	2
jagadeesh	4	1	10	2	1	1	1	1	1	1	1	2	2	1	2	2	2
ajimath hussain	5	1	12	1	1	2	2	1	2	1	1	2	2	1	1	1	2
sarala	3	2	15	2	1	2	1	2	1	1	1	1	2	2	2	1	2
adhina brassi	4	2	5	2	2	1	1	1	1	1	2	2	2	2	2	2	2
hussaina	5	2	10	2	1	2	2	2	2	2	1	2	1	2	2	2	2
madhivanan	5	1	9	2	1	2	1	2	2	1	1	2	2	2	1	2	2
kulandai velu	6	1	6	2	2	2	2	2	2	1	2	2	2	2	2	2	2
velraj	7	1	4	2	1	1	1	2	1	1	1	1	1	2	2	2	2
mariyamilton	4	1	8	2	2	1	2	1	2	1	2	2	2	2	2	2	2
kalyani	9	2	9	1	1	1	2	1	2	1	1	1	1	2	2	1	2
vasudevan	6	1	13	1	1	1	2	1	1	1	1	2	2	1	2	2	2
anil	5	1	7	1	2	2	2	1	2	1	1	2	2	2	1	1	2
ellarasi	7	2	10	2	1	1	1	2	2	1	1	2	2	1	2	2	1
kaleb	10	1	7	2	1	1	2	2	2	1	1	2	2	2	1	2	2
gomathy	5	2	6	2	1	2	1	1	1	1	1	2	2	1	1	2	2
basuddin	4	1	4	1	1	1	2	1	1	1	1	1	2	1	2	2	1
manikadevi	9	2	8	2	1	1	1	2	2	1	2	2	2	2	1	2	2
chandru	6	1	9	1	1	1	2	1	1	1	1	2	2	2	2	2	2
vadivelu	10	1	4	1	1	1	1	1	1	1	1	2	1	1	2	1	2
urmilla	4	2	9	2	1	1	2	1	2	2	2	2	2	2	1	2	2
zuwairiya	5	2	16	2	1	1	2	1	2	2	1	2	2	2	1	2	2
marimuthu	6	1	7	2	1	2	1	2	1	1	1	2	2	2	2	2	2
deric	5	1	6	1	1	2	2	1	1	2	2	1	2	1	1	2	2
reshma	8	2	4	2	1	1	2	1	2	2	2	2	2	2	1	2	2
danny	5	1	5	2	2	1	2	2	2	2	1	2	2	1	1	2	2
sami ul sa adhi	3	1	6	1	1	2	1	1	2	2	2	2	2	2	2	1	2
santhi	5	2	9	2	1	2	1	1	2	1	1	2	2	2	2	2	2
tamilarasan	6	1	8	2	1	1	1	2	2	2	1	2	2	2	1	2	2
vetrivel	7	1	5	2	2	2	2	2	1	1	2	2	1	1	1	2	2
prabhu	9	1	13	2	1	1	2	2	2	1	1	2	2	1	2	1	2
mubarakali	5	1	7	2	1	2	2	2	2	2	1	2	2	1	2	2	2
mathyas arthur	4	1	10	1	1	2	2	2	2	2	2	2	2	2	2	2	2
sekar	8	1	7	2	1	1	2	2	1	1	1	2	2	1	2	2	2
samyuktha	4	2	10	2	1	2	1	1	2	1	2	2	2	2	1	2	2
revathi	5	2	5	2	1	2	2	1	1	2	2	1	2	2	2	2	2
junaith	3	1	5	1	1	2	1	2	2	1	1	2	2	2	2	2	2
vasuki	6	2	9	2	2	1	2	1	2	2	2	1	2	1	2	2	2
monish	5	1	6	2	2	1	2	1	2	2	2	1	2	2	2	2	2
neelesh	5	1	11	2	2	1	1	2	2	1	2	1	2	2	2	2	2
mirudhulasri	6	2	4	2	1	2	1	2	1	2	1	2	2	1	2	2	2
stellarani	8	2	12	1	1	1	2	1	2	1	1	2	1	2	1	2	1
immanuuel	4	1	6	2	1	2	2	2	2	1	2	1	2	2	1	2	2
divinesh	5	1	8	1	2	2	2	2	1	1	1	1	2	2	2	2	2
sabika	6	2	20	2	1	2	1	1	2	2	2	1	2	2	2	2	2
joshwa	4	1	12	2	1	2	1	1	2	2	2	1	2	1	1	2	2
monikasri	4	2	8	2	1	2	1	1	2	1	1	1	1	1	1	1	2
jeyalaxmi	11	2	10	1	1	1	1	1	2	1	1	1	2	2	2	2	2
kamalesh	6	1	4	2	1	2	1	2	2	2	2	1	2	2	1	2	2
yogalaxmi	5	2	11	2	1	2	2	2	2	2	1	2	2	2	2	2	1
ashwanth	6	1	5	1	1	1	2	2	1	2	2	1	2	1	2	2	2
manoj	7	1	15	2	2	2	2	1	2	1	1	2	2	1	1	2	2
suganraj	8	1	10	2	1	1	1	2	2	2	1	1	2	2	2	1	2
rizwan	5	1	10	2	1	1	2	1	2	2	1	2	2	2	1	1	2
hathisan	4	1	5	2	2	2	1	1	2	2	2	2	2	1	1	2	2
nandhakumar	6	1	14	2	1	2	2	1	2	1	1	2	1	1	1	2	1

MASTER CHART

subamagalwai	9	1	20	2	2	2	1	1	1	2	1	1	1	1	2	2	2
sai rosini	5	2	11	2	1	2	1	1	2	1	1	1	2	1	2	2	2
sivaranjani	11	2	13	1	1	2	2	1	2	1	1	1	2	2	1	2	2
kevin	10	1	9	2	2	2	1	2	2	2	2	2	2	2	1	2	2
deep mondal	9	1	7	2	2	2	1	2	2	1	1	2	2	2	1	2	2
niraimathi	3	2	21	2	2	2	2	1	1	2	2	1	1	2	2	1	2
boojith	12	1	10	2	1	1	2	2	2	2	1	2	2	2	2	2	2
lithika	4	2	10	2	1	2	2	2	1	2	1	2	2	2	1	2	2
moshika	6	2	7	2	2	2	1	2	1	2	2	2	2	1	2	2	2
anjel	6	2	6	1	1	2	1	1	2	2	2	2	2	2	1	2	2
anish	8	1	8	2	2	1	2	2	2	1	1	1	2	1	1	2	1
manikandan	8	2	10	1	1	2	2	2	1	1	1	2	2	2	1	2	2
venda	10	2	5	2	2	2	1	2	2	1	1	2	1	1	2	2	2
dhanush	11	1	8	2	2	1	1	2	2	2	2	2	2	1	2	1	2
mithilesh	5	1	12	2	1	2	1	2	2	1	1	2	2	1	1	2	2
gopikrishnan	5	1	4	2	2	2	1	2	2	2	1	2	2	1	2	2	2
gokulakannan	7	1	5	2	2	2	2	2	2	2	1	2	2	1	1	2	2
gudikarthick	9	1	8	2	1	1	1	1	1	1	1	1	2	1	2	2	2
rachel	5	2	7	2	1	2	1	2	1	2	1	1	2	2	1	2	2
rubesh	4	1	9	2	1	2	1	2	2	1	1	2	2	2	2	2	2
irfan	5	1	7	1	1	2	1	1	2	1	2	2	2	1	1	2	2
ingarsal	9	1	8	2	1	1	1	2	2	2	1	1	1	1	2	2	2
jafarullah	11	1	16	1	1	1	1	1	2	1	1	2	1	2	1	2	2
harisaran	7	1	6	2	1	1	2	1	2	2	1	2	2	1	1	2	2
muskan	6	2	10	2	1	2	1	1	2	2	2	2	2	2	1	1	1
narayanareddy	8	1		2	1	2	2	1	1	1	1	2	2	1	1	2	2
surendar	6	1	10	2	1	1	2	2	2	2	1	2	1	1	2	1	2
munuraj	10	1	11	2	1	2	1	1	1	2	1	2	2	2	2	2	2
mannarmannan	8	1	11	2	2	2	2	2	1	1	1	2	2	1	2	2	2
maheshwari	6	2	5	2	2	1	1	1	2	2	1	1	1	1	2	2	2
varsini	7	2	9	1	2	2	1	1	2	1	1	1	1	1	1	1	2
priyadarsini	8	2	14	2	2	1	2	2	2	2	1	1	2	1	1	2	2
kanish	4	1	6	1	1	2	1	1	2	2	2	2	2	2	2	2	2
sabarsh	6	1	8	2	1	2	1	2	1	2	2	2	2	1	1	2	2
jersi	5	2	5	2	2	2	2	2	2	2	1	2	2	1	1	2	2
merceline grace	7	2	9	1	1	2	2	2	2	1	1	1	2	2	2	2	2
vimal	6	1	6	2	1	2	2	2	2	2	1	2	2	2	1	2	2
vinodhini	7	2	8	2	1	2	2	1	2	2	1	2	2	1	1	1	2
xavier	8	1	5	2	1	2	1	2	2	2	1	2	2	2	2	2	2
abdul salam	8	1	7	2	2	2	1	1	2	2	1	2	2	2	1	2	2
gayathri	9	2	13	1	1	1	2	2	2	2	1	1	1	2	2	2	2
boobesh	3	1	6	2	1	2	1	2	2	1	2	2	2	2	1	1	2
charu	10	2	13	2	2	1	2	1	1	2	2	1	2	2	1	2	2
yogitha	6	2	9	2	2	1	1	2	2	2	2	2	2	1	1	2	2
roobanandhini	8	2	4	2	1	2	1	2	2	2	2	2	2	2	1	2	1
usha	6	2	8	2	2	2	2	1	1	2	1	2	2	2	2	2	2
renuka	5	2	7	2	1	2	2	1	1	2	2	2	1	1	2	2	2
kedharnath	7	1	10	1	2	1	2	2	2	2	2	2	2	1	1	2	2
naga	4	1	7	2	1	2	1	2	2	2	2	1	2	2	1	2	2
balasundhari	5	2	10	2	1	2	2	1	2	2	1	2	2	1	1	1	2
vasimkhan	5	1	13	2	1	2	1	2	2	2	2	2	2	2	2	2	2
madhan	6	1	5	2	2	2	2	1	2	2	2	2	2	2	2	2	2
benjamin	8	1	11	2	1	1	2	1	2	1	1	1	2	1	2	2	2
visalakshi	7	2	6	2	2	1	1	2	2	1	1	2	2	2	1	2	2
kamatchi	11	2	15	2	1	1	2	1	2	1	1	2	2	1	2	2	2
prema	9	2	10	2	2	1	2	1	2	1	1	2	2	2	1	2	2
biju	4	1	5	1	2	2	2	2	2	2	1	2	2	2	1	2	2
munna	4	1	9	2	1	2	1	1	1	2	2	2	2	1	2	2	2
Balamurali	9	1	7	1	1	1	2	2	2	1	1	2	2	1	1	2	2
shyam	7	1	14	2	1	2	2	1	1	2	1	2	2	2	1	2	2
sundhari	9	2	10	2	1	2	1	1	2	1	2	2	2	2	1	2	2
sumathi	6	2	7	2	2	2	1	2	2	1	1	2	2	1	1	2	2
wagitha begam	6	2	11	2	1	1	2	1	1	2	2	2	2	2	1	1	1
diana	5	2	7	2	1	2	1	2	2	1	2	1	2	2	1	2	2
elumalai	6	1	8	2	2	1	2	2	2	1	2	1	2	2	1	2	2
evanjalin	7	2	7	2	2	1	2	1	2	2	2	2	2	1	2	2	2

MASTER CHART

josaf	6	1	14	1	1	2	2	1	2	2	1	1	2	1	1	2	1
dhoni	6	1	6	1	1	2	1	1	2	1	1	2	2	2	2	2	2
sana	5	2	6	2	1	2	1	2	2	2	2	1	2	2	2	2	2
wilson	6	1	10	2	1	2	1	2	2	1	2	1	1	1	2	2	2
agoramurthy	9	1	12	2	2	1	2	1	1	2	1	2	2	2	2	2	2
senthil	7	1	18	2	2	2	1	1	1	2	2	2	2	2	1	2	1
vadivu	8	2	12	2	2	1	2	1	2	2	1	1	2	2	2	2	2
kamesh	5	1	10	1	1	2	1	1	2	1	1	1	1	1	1	2	2
kanimozhi	7	2	11	1	2	1	1	2	1	2	1	2	2	1	1	1	2
kiran	10	1	5	2	1	2	1	1	2	2	2	2	2	1	1	2	2
nirmal	10	1	4	2	1	2	2	1	2	2	2	2	2	2	2	2	2
lithika	5	2	7	2	2	2	1	1	1	2	2	2	2	2	2	2	2
rishibharathi	4	1	6	2	2	2	1	1	1	1	2	1	1	2	1	2	2
saikumar	9	1	14	2	1	1	2	1	1	2	2	2	1	1	1	2	2
dharshitha	3	2	4	2	2	2	1	1	1	2	2	2	2	2	2	2	2
prithisha	4	2	13	2	1	1	1	1	1	1	1	2	2	2	2	2	2
dhanush	8	1	11	1	1	1	1	1	1	1	1	2	1	1	1	2	2
dharsini	9	2	20	2	2	2	1	2	1	1	2	2	1	2	1	2	2
kevinbharathi	3	1	21	1	1	1	1	1	1	1	2	1	1	2	1	2	2
balakrishnan	4	1	7	2	1	2	1	2	1	1	2	1	2	2	2	2	2
sunitha	10	2	10	2	1	2	2	2	2	1	1	2	2	1	2	2	2
mozhi arasi	5	2	6	1	1	1	1	1	2	1	2	1	2	2	1	2	2
jackson	3	1	6	2	1	2	1	1	2	1	1	2	2	1	1	2	2
prajan kumar	3	1	10	2	2	2	2	1	2	2	2	2	2	2	1	2	2
santhosh	10	1	5	2	1	2	1	1	2	1	1	1	2	2	1	2	2
velmurugan	10	1	20	2	2	2	1	1	2	2	1	2	2	1	2	2	2
stellamary	9	2	30	2	2	2	1	2	1	2	1	2	2	1	1	2	2
abinaya	5	2	15	2	2	1	1	2	2	2	2	1	2	2	1	2	2
niranjan	12	1	9	2	2	2	2	2	1	1	1	1	2	1	2	2	2
venkataraman	8	1	9	2	2	2	2	2	2	2	2	2	2	2	2	2	2
srimathi	3	2	8	1	1	1	2	1	2	2	1	2	2	2	1	2	2
deepika	6	2	7	2	1	1	2	1	1	1	1	1	2	2	2	2	2
sameera	11	2	14	2	2	1	2	2	2	1	1	2	2	2	2	2	2
pachayappan	3	1	8	2	2	2	1	1	1	2	2	1	2	2	1	2	2
hemanth	12	1	20	2	2	1	2	1	1	2	2	2	2	2	2	1	2
sharmi	8	2	7	2	1	1	2	2	2	2	2	2	2	2	1	2	2
janani	7	2	6	1	1	2	1	2	1	1	1	1	1	2	1	2	2
valarmathi	8	2	5	2	2	1	1	2	2	2	2	2	2	2	1	2	2

MASTER CHART

SGOT NORMAL OR ELEVATED	SGPT NORMAL OR ELEVATED	WIDAL	TYPHIDOT	ENTERIC CULTURE	AMPICILLIN	AMIKACIN	CIPROFLOXACIN	CEFOTAXIM	CEFTRIAXONE	CHLORAMPHENICOL	NALIDIXIC ACID	COTRIMOXAZOLE	FEVER DEFERVESCENCE	NO SIGNIFICANT CHANGE
1	1	1	2	2									5	
1	1	2	2	2									4	
1	1	2	2	2									5	
1	1	1	2	1	2	2	1	1	1	2	2	2	4	2
2	2	2	1	2									13	1
1	1	1	2	2									4	
1	1	2	2	2									5	1
1	1	2	1	2									3	
1	1	2	2	2									6	
1	1	1	1	1	2	1	2	1	1	2	1	1	7	
1	1	2	2	2									7	2
1	1	2	2	2									4	
1	1	1	1	2									3	1
1	1	2	2	2									5	
1	1	2	2	2									5	
2	2	1	1	2									3	2
1	1	2	2	2									4	
2	2	1	1	1	2	1	1	1	1	2	2	2	7	2
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MASTER CHART

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MASTER CHART

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